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THE EXPERIMENTAL SIMULATION IN THE DOG OF THE CYANOSIS AND HYPERTROPHIC OSTEOARTHROPATHY WHICH ARE ASSOCIATED WITH CONGENITAL HEART DISEASE

MILTON MENDLOWITZ, M.D., AND ALAN LESLIE, M.D.
NEW YORK, N. Y.

THE fundamental disturbance in the cyanotic form of congenital heart disease is a shunt of unaerated blood into the systemic circulation. The purpose of our experiments was to establish such a shunt and to study the resulting circulatory and skeletal changes.

Many attempts have been made to establish fistulae between vessels containing aerated and unaerated blood. For example, anastomoses have been made between systemic artery and vein[1] and systemic artery and pulmonary artery.[2] Fistulae have also been created between the left and right auricles or ventricles.[3] It is apparent, however, that, at the sites of these anastomoses, aerated blood is at a higher pressure than unaerated blood. Since blood flow is always in the direction of lower pressure, aerated blood is introduced into the pulmonary arterial circulation, but no unaerated blood enters the systemic arterial circulation. There can consequently be no cyanosis.

Up to the present time, there has been no established method of shunting unaerated blood into the systemic circulation. In such a shunt, the pressure in the vessel carrying unaerated blood must exceed the pressure in the vessel carrying aerated blood. Such a pressure relationship is not found in the greater circulation. It does exist, however, in the lesser circulation, in which the best site for an anastomosis is at the place of contiguity of the pulmonary artery and the left auricle. After many unsuccessful trials, we were able to establish this anastomosis in four dogs.

From the Laboratories of The Mount Sinai Hospital, New York.
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PROCEDURE

Mongrel dogs, weighing from 13 to 25 kg., were used. Studies were made one or two weeks before operation, several weeks after operation, and subsequently at approximately trimonthly intervals. These studies were carried out under sodium pentobarbital anesthesia, and included measurements of oxygen consumption, cardiac output, blood volume, ether and cyanide circulation time, and arterial and venous blood pressure. Roentgenograms of the anterior extremities were made from time to time. Diodrast study of the heart by the method of Robb and Steinberg[4] was carried out on one dog. Post-mortem examinations were made on all animals.

The operative technique, described briefly in preliminary reports,[5, 6] is now presented completely and with several modifications, as follows. After the dog is anesthetized with sodium pentobarbital, a metal cannula is passed transorally into the trachea. Escape of air around the cannula is prevented by inflating a narrow cuff at the tracheal end through a side tube in the cannula. The dog is then placed

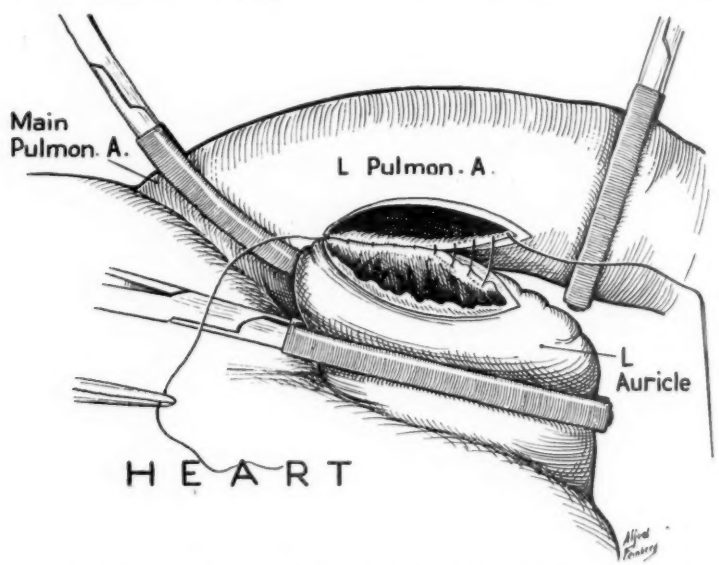

Fig. 1.—Anatomic relationships and detail of suture anastomosis.

on its right side. A sandbag is placed under the right upper anterior part of the chest. The left and right forepaws are secured above the animal's head and the hindpaws are fastened in such a way as to make the abdomen horizontal. The chest is thereby fixed in an oblique position. The incision is made in the middle of the fourth intercostal space, extending from a point 2 cm. lateral to the sternum to the edge of the long spinal muscles. Because an anticoagulant is used after operation, special care is taken to insure thorough hemostasis. After the pleura is opened, artificial respiration is carried on through the tracheal cannula by intermittent positive pressure insufflation. The ribs are then separated by a self-retaining retractor. The left lung is compressed toward the spine under wet gauze packs held in place by a retractor. An incision is then made in the pericardium, posterior and parallel to the left phrenic nerve, exposing the pulmonary artery and its left main branch, as well as the left auricle. The left pulmonary artery is dissected free, and a heavy silk ligature is passed beneath it for traction. A rubber-covered curved clamp is then applied to the main and left pulmonary artery, with its points directed toward the lung. The left pulmonary artery distal to the clamp is occluded

by the application of a short, straight, rubber-covered, intestinal clamp. If these maneuvers have been properly executed, there is now an isolated section of artery adjacent to the upper edge of the left auricular appendage. The blood flow to the left lung is completely interrupted, but the right lung receives blood which flows under the curved clamp into the right pulmonary artery. A short, straight, rubber-covered, intestinal clamp is then applied to the base of the left auricular appendage, parallel to the curved clamp on the artery, in such a way that the auricular edge is apposed to the isolated segment of artery. Parallel longitudinal incisions, approximately the length of the diameter of the left pulmonary artery, are now made in these structures. After the suture, the diameter of the anastomosis becomes about 50 to 75 per cent of the length of the incision.

Vaselinized, six-0, arterial silk, on a straight, atraumatic needle, is used for the anastomosis. An everting, running, mattress suture is used, the technique of which is illustrated in Fig. 1. Before the suture is tied, the anastomosis is filled with physiologic saline solution. The auricular clamp, distal arterial clamp, and curved clamp are removed in the order named. If the anastomosis has been successfully established, the auricular appendage is seen to balloon out during ventricular systole, and, if the auricle is palpated gently, a systolic thrill is easily felt.

The pericardium is then closed by two or three interrupted sutures, and the ribs brought together by two heavy silk sutures, each passed around the rib above and below the incision. The muscles are then approximated by running sutures, and the air in the pleural cavity is "blown off" before final closure. Artificial respiration is then stopped, and, finally, the skin incision is closed by a running suture, reinforced by one or two tension sutures. Silk is used throughout.

The postoperative administration of an anticoagulant prevents thrombosis at the fistula. In some experiments heparin[7] was used. An initial dose of 0.4 mg. per kilogram was given, followed by the continuous intravenous administration of 0.2 mg. per kilogram per hour for three days. In other experiments, Chlorazol Fast Pink, BKS, purified by the method of Modell,[8] was used; 0.5 c.c. per kilogram of a 5 per cent solution was administered intravenously immediately after operation, and this dose was repeated three times a day for three days. Larger doses were found to be toxic for these animals. Although heparin was less toxic, the dye was cheaper and its action more prolonged.

Certain precautions must be observed to insure success. Animals in poor condition should not be subjected to this extensive operation, which predisposes to pulmonary complications. If air is trapped in the anastomosis, there may be sudden death from air embolism, for the lungs no longer intervene between the pulmonary artery and left auricle. This is avoided by filling the anastomosis with physiologic salt solution before tying the suture. Thrombosis is avoided by careful endothelial approximation and by the administration of an anticoagulant. Hemorrhage, on the other hand, is avoided by painstaking and complete hemostasis and by careful regulation of the dosage of anticoagulant. The strictest asepsis is necessary. The dressing must be applied firmly enough for moderate local compression without compromising respiratory excursion. If postoperative pulmonary infection is suspected, sulfathiazole should be administered.

MEASUREMENTS AND CALCULATIONS

The mean arterial blood pressure was measured directly by femoral artery puncture, and the venous blood pressure, by direct puncture of the external jugular vein. The circulation time was measured with ether and cyanide, and the blood volume was ascertained by a modification of the dye method. The oxygen consumption was measured by means of a basal metabolism apparatus attached to a tracheal cannula. The oxygen content of the arterial (femoral), saturated arterial, and mixed venous

(right heart) blood was determined in duplicate by the method of Van Slyke and Neill.[9] The right heart blood was obtained by direct puncture. The oxygen content of the saturated arterial blood was an accurate index of the blood hemoglobin. The percentage oxygen saturation of the arterial blood was calculated. The details of all these procedures have been described previously.[10]

Before the shunt is established, the cardiac output, according to the Fick principle,[11] equals

$$100 \frac{\text{oxygen consumption in c.c. per minute}}{\text{A-V difference in vol. per cent}}.$$

This represents the pulmonary volume flow in c.c. per minute, which in this case is identical with the output of the right ventricle. Since the two ventricles must expel equal quantities of blood over any period of time, the total cardiac output is twice that of the right ventricle. Communications between bronchial and pulmonary vessels and the oxygen consumed in pulmonary metabolism are not included in the calculations. These factors, however, are probably negligible.

After the shunt is established, the total cardiac output is again equal to twice the univentricular output. The left ventricular output now equals the pulmonary volume flow *plus* the volume flow through the shunt. The pulmonary volume flow, P, can be calculated from the formula,

$$P = 100 \frac{\text{oxygen consumption (in c.c. per minute)}}{\text{A-V difference (in vol. per cent)}}.$$

In the calculation of the A-V difference, the oxygen content of the mixed venous blood is determined, as before, on the sample obtained by right heart puncture. The oxygen content of the arterial blood, however, cannot be determined directly on the sample obtained by femoral artery puncture because this contains shunted unaerated blood, as well as aerated blood. To calculate the oxygen content of aerated blood, such as issues from the pulmonary veins, the oxygen content of the saturated arterial blood is multiplied by the preoperative percentage saturation of the arterial blood. This is justifiable because, with the animal breathing pure oxygen, the preoperative percentage saturation of the arterial blood varies between the narrow limits of 96 and 99 per cent, and because there is no postoperative impairment of blood aeration in the lungs. There should therefore be no significant variation in the percentage saturation of the postoperative, as compared with the preoperative, pulmonary vein (aerated) blood.

The volume flow through the shunt is calculated from a formula derived as follows:

Let x = c.c. of shunted blood in 100 c.c. of femoral arterial blood; $\therefore$ $100 - x$ = c.c. of aerated blood in 100 c.c. of femoral arterial blood; a = oxygen content of femoral arterial blood in vol. per cent; b = oxygen content of shunted (right heart) blood in vol. per cent; c = oxygen content of pulmonary vein (aerated) blood in vol. per cent. Then, $\frac{bx}{100}$ = c.c. oxygen in x c.c. of shunted blood; and, $\frac{c(100 - x)}{100}$ = c.c. oxygen in $100 - x$ c.c. of aerated blood. Since the oxygen content of 100 c.c. of femoral arterial blood must equal the sum of the oxygen contents of x c.c. of shunted blood and of $100 - x$ c.c. of aerated blood,

$$\frac{bx}{100} + \frac{c(100 - x)}{100} = a;$$

or,

$$x = \frac{100(a - c)}{b - c}.$$

This represents the percentage of shunted blood in the femoral arterial blood sample and $100 - x$ represents the percentage of aerated blood.

Since each 100 c.c. of blood expelled by the left ventricle contain x c.c. of shunted blood, and since the minute volume flow of blood not shunted (pulmonary volume flow), P, is known (see above), the minute volume flow through the shunt, S, may be calculated as follows:

$$S : P :: x : 100 - x;$$

$$S = \frac{Px}{100 - x}.$$

The left, and consequently the right, ventricular output, therefore, equals S + P.

RESULTS

Many of the experiments were unsuccessful. There was an immediate operative mortality due to accident or over-anesthesia. Many animals died because of pre-existing distemper or worms, which rendered them incapable of surviving so extensive an operation. Before proper precautions were taken, death from air embolism occurred occasionally. If the anastomosis was made too large, the consequent sudden and profound anoxemia was sometimes fatal. Postoperative pulmonary or pleural infection was not uncommon, and was probably due to the prolonged ischemia of the left lung at operation, predisposing it to infarction and subsequent infection. Pneumothorax and pleural fistula were occasional fatal complications brought about by improper closure of the chest or by wound infection. If too much anticoagulant was used or if hemostasis was inadequate, there was wound and intrathoracic hemorrhage, with or without superimposed infection. In the early experiments, when the fistula was made between the left pulmonary artery and vein, thrombosis was the rule because of angulation of the vein and because of the necessarily small size of the anastomosis. Thrombosis also occurred in the later experiments if approximation of intima to endocardium was not exact, or if too little anticoagulant was used. In one experiment, the observations demonstrated progressive narrowing and final occlusion of the anastomosis by thrombosis. Occasionally, detachment of a thrombus caused embolism in the systemic circulation. In one experiment, bacterial endocarditis was found at autopsy and was probably caused by infection of a thrombus at the anastomosis.

The results in the four successful experiments are summarized in Table I. There were no significant alterations in the arterial or venous blood pressure or in the ether circulation time. The cyanide circulation time, however, was definitely decreased in all the experiments. The percentage oxygen saturation of the arterial blood was also uniformly decreased. The greatest shunt was 47 per cent, and the smallest, 14 per cent. In the animals in which more than one postoperative study was made, there were small variations in the percentage shunt, probably because of variations in the pulmonary arterial pressure. The cell volume was increased in three of the four animals and the total blood volume was increased in the animal with the largest shunt. The hemoglobin (saturated arterial blood oxygen) rose significantly in only one dog (No. 335).

TABLE I

DOG NO.	237		262				294				335	
Time	2 WEEKS PREOP.	3 MONTHS POSTOP.	2 WEEKS PREOP.	1 MONTH POSTOP.	7 MONTHS POSTOP.	10 MONTHS POSTOP.	1 WEEK PREOP.	2 MONTHS POSTOP.	4 MONTHS POSTOP.	6 MONTHS POSTOP.	2 WEEKS PREOP.	3 MONTHS POSTOP.
Weight (kg.)	17.1	17.1	20.0	19.0	22.5	22.0	19.4	18.4	18.8	20.0	15.3	14.0
Arterial blood pressure (mm. Hg)	140	100	135	122	155	142	130	135	160	130	96	115
Venous pressure (cm. water)	0	1.0	2.0	3.5	2.0	4.0	2.0	2.3	2.5	2.0	0	3.0
Ether time (sec.)	4.0	3.0	2.5	3.5	3.0	2.5	2.5	3.0	-	4.0	-	-
Cyanide time (sec.)	9.0	5.0	7.0	6.0	5.5	4.5	6.5	4.0	5.0	5.0	8.0	6.0
Blood volume (c.c.)	1390	1600	2579	2254	2521	2331	2139	2031	2183	2091	1825	1786
Plasma volume (c.c.)	750	850	1625	1375	1563	1375	1250	1300	1375	1150	1150	1000
Cell volume (c.c.)	640	750	954	879	958	956	869	731	808	941	675	786
Arterial blood oxygen (vol. %)	22.15	16.51	16.57	16.39	16.68	15.48	19.11	12.90	17.0	17.21	15.92	17.54
Venous blood oxygen (vol. %)	15.57	11.62	13.92	14.05	12.75	12.65	15.88	10.19	14.02	14.33	12.99	14.32
Saturated blood oxygen (vol. %)	22.37	21.02	16.73	17.48	17.46	16.64	19.50	13.75	17.98	18.69	16.52	19.67
% saturation of arterial blood	99.0	78.3	99.0	93.7	95.5	93.0	98.0	93.8	94.5	92.1	96.5	89.2
Oxygen consumption (c.c. per min.)	117	120	144	130	153	127	113	110	127	128	108	95
Systemic blood flow (c.c. per min.)	1780	2478	5420	5537	3835	4487	3500	4057	4264	4443	3686	2951
Pulmonary blood flow (c.c. per min.)	1780	1318	5420	3987	3310	3325	3500	3343	3527	3208	3686	2039
% shunt	0	47	0	28	14	26	0	18	17	28	0	31
Autopsy findings	Died 4 months postop. Widespread pneumonia; anastomosis patent (8 mm.).		Died 11 months postop. Widespread pneumonia; anastomosis patent (4 mm.); pedunculated thrombus extending into auricle.				Sacrificed 8 months postop. Anastomosis patent and fenestrated, one opening (4 mm.) separated by thin septum from second opening (2 mm.); subperiosteal bone proliferation in long bones.				Died 4 months postop. Anastomosis patent (6 mm.); pedunculated thrombus in auricle and thrombus partially occluding left pulmonary artery distal to anastomosis; cerebral embolus.	

In the other three, it remained essentially unchanged, except for a transient postoperative anemia in one (No. 294). The systemic blood flow always exceeded the pulmonary blood flow by the volume flow through the shunt. The pulmonary blood flow was either decreased or unchanged in all four experiments. The systemic blood flow was increased in two animals and decreased in the other two. In dog No. 294 the increased systemic blood flow might have been due in part to the transient anemia. However, the cardiac output became still greater as the anemia subsided. The changes in systemic blood flow were not caused by changes in the metabolic rate, inasmuch as the oxygen consumptions remained essentially unaltered. Hypertrophic osteoarthropathy was found by roentgenologic examination (Fig. 2) in one of the two dogs with increased systemic blood flow. In none of the other animals were such bone changes found.

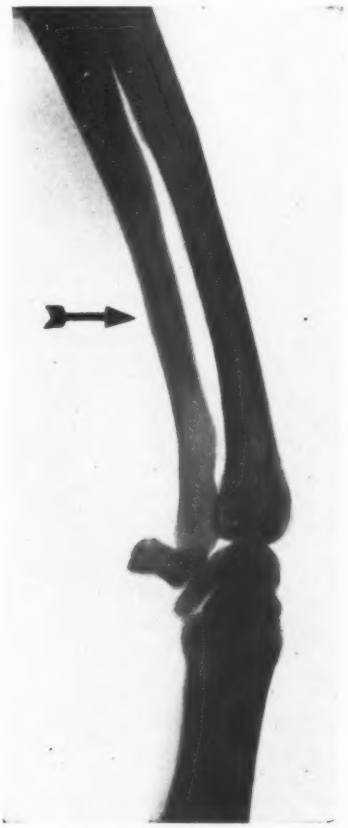

Fig. 2.—Roentgenogram of radius and ulna of dog No. 294, showing periosteal proliferation (arrow).

Isolated observations not recorded in Table I were made on several animals. Pulse rates and respiratory rates did not vary significantly. In several dogs, the heart rate and the arterial blood pressure were recorded before and after manual compression of the anastomosis at

operation. Closing the anastomosis slowed the heart and increased the blood pressure, whereas releasing the compression caused opposite changes. This effect, however, was slight, probably because of the suppression of reflexes by the anesthetic and by operative shock. A soft systolic murmur could be heard in some animals. It must be remembered that the pressure in the pulmonary artery is low, and that the intensity of a murmur would therefore be less than that of a murmur coming from the systemic circulation. Cyanosis of the tongue was observed in all the successful experiments; the degree was proportional to the size of the shunt. Increased intensity of the cyanosis after exercise or excitement was observed frequently, and was probably caused by increased pressure in the pulmonary artery, with consequent increase in the percentage shunt, and also by increased oxygen "unsaturation" of the mixed venous blood. In one animal the patency of the anastomosis was demonstrated ante mortem by the injection of diodrast.

Fig. 3.—Comparison of ulna of dog No. 294 (left) with ulna of normal dog (right).

Two of the dogs died of fulminating pneumonia four and eleven months, respectively, after operation. One animal died of a cerebral embolus, four months after operation. The source of this was a thrombus extending from the anastomosis into the auricle. The remaining dog was sacrificed eight months after operation. In all the autopsies

the anastomoses were found to be patent and their cross-section areas were proportional to the calculated percentage shunts. The largest fistula was found in the dog with the 47 per cent shunt. It admitted a lead pencil with ease. In two of the animals there was no thrombus at the site of the fistula. In the other two there were thrombi extending from the edge of the anastomosis into the auricle, and, in one of these, an additional thrombus extended from the anastomosis into the left pulmonary artery. In dog No. 294 the presence of hypertrophic osteoarthropathy was confirmed at autopsy (Figs. 3 and 4). No bone changes were found in the other dogs. Fig. 5 shows the opened main and left pulmonary artery, the orifice of the right pulmonary artery, and the patent anastomosis of dog No. 262.

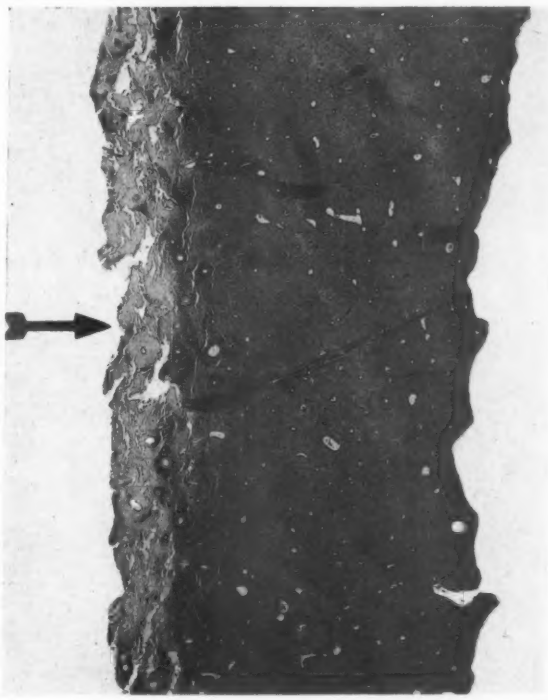

Fig. 4.—Photomicrograph of transverse section of tibia of dog No. 294, showing new-formed periosteal bone.

DISCUSSION

It is apparent from these experiments that it is possible to establish a permanent fistula between the pulmonary artery and the left auricle in dogs. Such a fistula reproduces the circulatory changes found in most cases of congenital heart disease with cyanosis,[12] as typified by the tetralogy of Fallot.

When there is an abnormal communication between vessels carrying aerated and unaerated blood, there is an increase in volume flow through

the circuit in which the pressure is lower at the site of the shunt, at the expense of the circuit in which the pressure is higher. With an arteriovenous fistula, for example, and also when the ductus arteriosus is patent, the lesser circulation not only carries all the venous return from the greater circuit, but also carries oxygenated blood shunted in from the systemic arteries. The total blood flow through the lungs is therefore greater than the total systemic blood flow. Conversely, in the cyanotic type of congenital heart disease and in our experiments, the direction of flow through the shunt is from the lesser to the greater circulation. The total systemic blood flow, therefore, exceeds the total pulmonary blood flow by the amount of blood shunted.

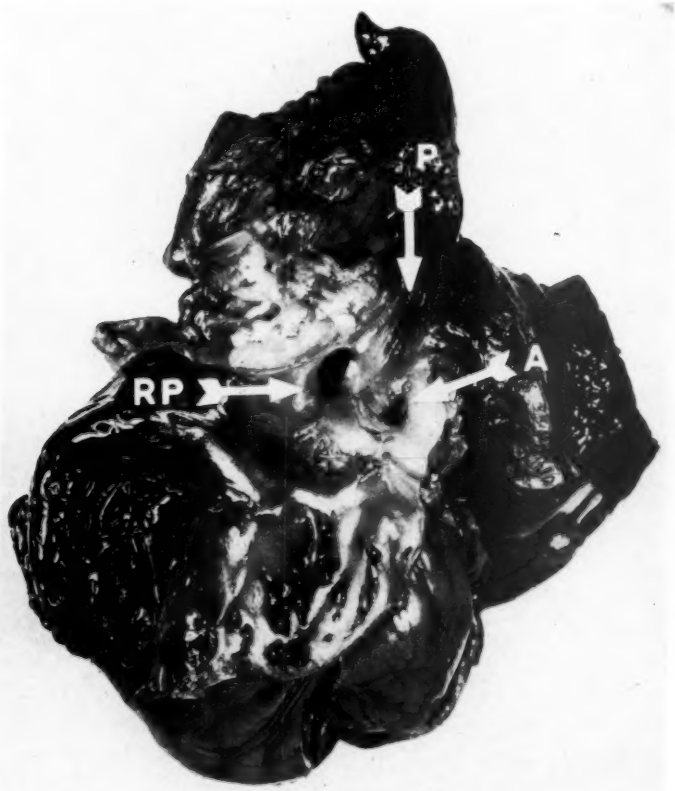

Fig. 5.—Heart of dog No. 262, showing opened right ventricle and pulmonary artery. RP, Right pulmonary artery orifice; LP, left pulmonary artery (opened); A, pulmonary artery orifice of anastomosis.

In addition to this relative increase in systemic blood flow, an absolute increase was also found in the two animals in which there were no obstructing thrombi. This increase in left ventricular output, as well as the increase in cell volume or total blood volume, is probably a mechanism which compensates for the chronic systemic arterial anoxemia. Because of such compensating mechanisms, the delivery of oxygen to

the tissues, in the resting state, at least, is normal despite the anoxemia, and the oxygen consumption remains unchanged. With exercise, these compensating mechanisms may break down, with ensuing tissue anoxia.

Hypertrophic osteoarthropathy has been known to occur in animals,[13-16] usually in the wake of pulmonary tuberculosis or pulmonary neoplasm, spontaneous or experimental. Attempts to reproduce these bone lesions in the experimental animal have been uniformly unsuccessful.[17-23] In our experiments, although the anastomosis between the pulmonary artery and the left auricle was made successfully in four dogs, only one of these developed hypertrophic osteoarthropathy. It may be of importance that only in this dog was there an absolute increase in systemic cardiac output, together with a survival period long enough for bone changes to develop. The cause of the bone proliferation was not anoxia, for, despite the arterial anoxemia, the transport of oxygen to the tissues was normal because of the increased blood flow, and the oxygen consumption remained unchanged. It is possible, however, that the chronically excessive systemic blood flow increased periosteal nutrition and thus stimulated bone proliferation. Since hypertrophic osteoarthropathy occurs in human congenital heart disease with cyanosis, it is possible that a similar mechanism is responsible for the development of the bone changes.

SUMMARY

1. A procedure for anastomosis of the pulmonary artery to the left auricle in dogs is described.

2. In the successful experiments, this procedure reproduced the circulatory derangements found in the cyanotic type of congenital heart disease.

3. In one experiment, hypertrophic osteoarthropathy developed, and was apparently attributable to increased systemic blood flow.

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THE CARDIOVASCULAR EFFECTS OF PAREDRINE

M. H. Nathanson, M.D., H. Engelberg, M.D., and J. Hersh, M.D.
Los Angeles, Calif.

PAREDRINE is the name which has been given to the new epinephrinelike compound, parahydroxyphenylisopropylamine. This substance stands between epinephrine and ephedrine in chemical structure, and, judging from its chemical composition, should possess a more intense sympathomimetic action than ephedrine. The action of this compound in the prevention of cardiac standstill has already been described by one of us (M. H. N.).[1] The purpose of the present communication is to report observations on both the cardiac and pressor actions of the substance, and to discuss therapeutic applications.

CARDIAC ACTION

Although epinephrine and related compounds affect various properties of the heart, we have been chiefly concerned with the action of these drugs on cardiac standstill for the following reasons: (1) The chief therapeutic indication for the sympathomimetic amines in heart disease is in the prevention and treatment of cardiac standstill, and (2) the effectiveness of drugs on cardiac standstill can be studied in man by an accurate and well-controlled method, previously described.[2] This method utilizes persons who have a sensitive carotid sinus, so that prolonged cardiac arrest can be consistently and repeatedly produced by pressure on the carotid sinus. In these cases, apparently because of overactivity of the vagus nerve, carotid sinus pressure eliminates the activity of the sinus node. The cardiac standstill is caused by temporary inactivity of the sinus node and by failure of development of secondary centers of impulse initiation. The indication that a drug is effective in the prevention of cardiac standstill is the abolition of the cardiac arrest either by the restoration of the activity of the sinus node or by the development of a new impulse initiating focus. The technique of the experiments is simple. An electrocardiogram is made during the period of cardiac arrest produced by carotid sinus pressure. The drug to be tested is then administered, and the carotid sinus pressure is repeated after suitable intervals. In a previous report[3] it was shown that a group of unrelated drugs, including barium chloride, calcium gluconate, digitalis, caffeine, coramine, metrazol, and thyroxine, had no

From the Department of Medicine, University of Southern California.
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influence on the induced cardiac standstill. It was then demonstrated that the only effective compounds were epinephrine and chemically related substances.[4] It was possible to ascertain the relative activities of various sympathomimetic amines by this method. In most instances the cardiac standstill was abolished by the development of a new pacemaker, usually in the ventricles. The reaction to varying doses of epinephrine was first ascertained, and it was found that the rate of impulse formation in the new pacemaker was proportional to the dose of the drug. The action of other sympathomimetic amines was then compared with that of epinephrine, and a ratio of activity was established. For example, the intravenous injection of 2 mg. of neosynephrine reproduced the effect of $\frac{1}{50}$ mg. of epinephrine, giving a ratio of activity of neosynephrine to epinephrine of 1 to 100. A number of sympathomimetic amines were studied by this method, and the comparative activity on cardiac standstill of the more important is given in Table I.

TABLE I

DRUG	APPROXIMATE RATIO OF ACTIVITY TO EPINEPHRINE
Cobefrine	1:10
Epinine	1:40
Adrenalone	1:40
Neosynephrin	1:100
Synephrin	1:400
Tyramine	1:1,200
Ephedrine	1:1,500

It was found that ephedrine was the only compound which was effective on induced cardiac standstill when given orally. However, large doses were necessary, and frequently the standstill was prevented only by amounts of the drug which produced unpleasant side effects. The observations of Alles[5] and Alles and Prinzmetal[6] indicated that paredrine was a stable sympathomimetic amine with greater activity than ephedrine. The effect of this drug has now been studied in sixteen cases in which cardiac standstill could be induced by pressure on the carotid sinus. The effective dose of the drug was 60 mg. in fourteen cases and 40 mg. in four, and in each instance the induced cardiac standstill was modified. The mechanism of the abolition of the standstill varied. In nine instances the standstill was abolished by the development of a rhythm which arose in or near the auriculoventricular node; in three, lower ventricular foci became active; in three instances the activity of the sinus node was restored; and in one case the rhythm consisted of sinus beats alternating with beats which arose from an ectopic ventricular focus. In five cases the activity of paredrine and ephedrine was compared, and paredrine was found to be between two and three times as effective as ephedrine. Four patients with spontaneous attacks of dizziness or syncope, associated with sensitivity of the carotid sinus,

have now been observed for periods of one year or more, and the attacks have been reduced in frequency, or eliminated, by doses varying from 40 mg. to 60 mg. three times a day (Fig. 1). The effect of the drug was also studied in six cases of heart block. In two of four cases of

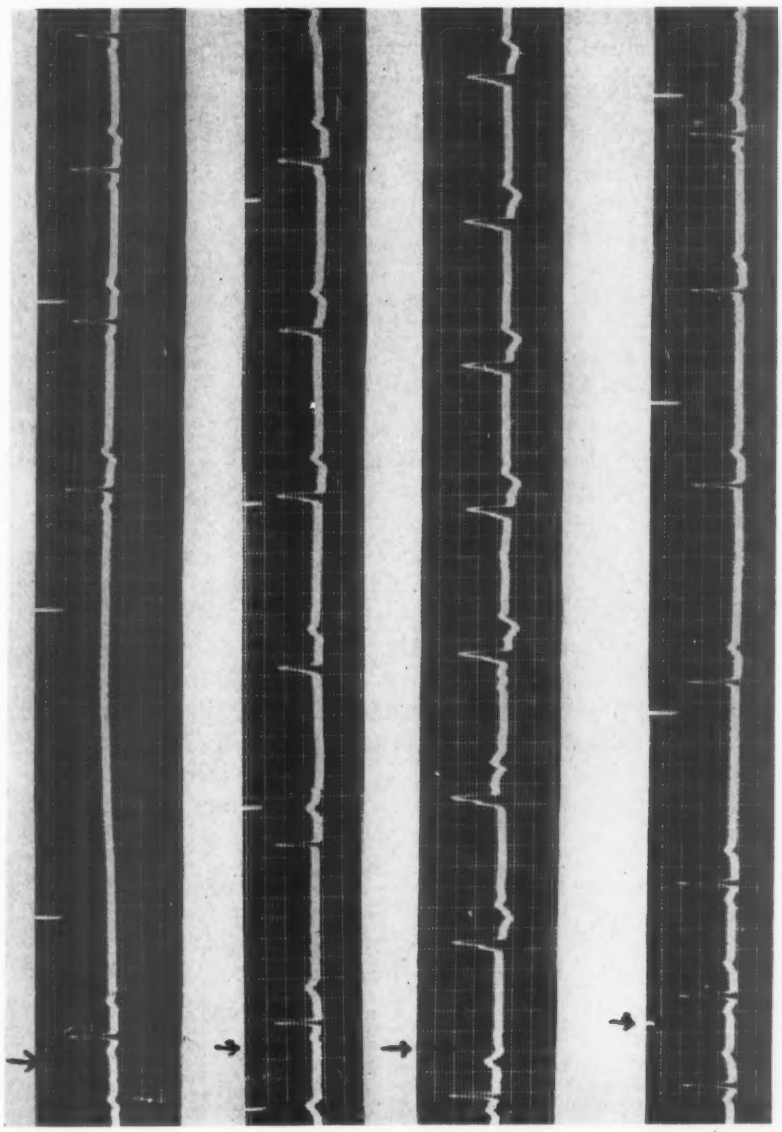

Fig. 1.—Patient I. K. History of frequent syncopal attacks which could be reproduced by pressure on the right carotid sinus. Upper strip shows standstill of five seconds induced by pressure on the carotid sinus (arrow). Lower strips show the effect of carotid sinus pressure thirty, sixty, and ninety minutes after the oral administration of 60 mg. of paredrine hydrobromide.

complete block, the latter was changed to partial block after 60 mg. of the drug. In two cases of complete block the ventricular rate was increased. In one instance of partial block (3 to 1), the block disappeared after the administration of 60 mg. three times a day for a week. In the other case of partial block the ventricular rate increased. Four patients

with chronic heart block have been followed for two years. Although they may be free of syncopal attacks for varying periods without therapy, these patients find it necessary to resume the use of the drug periodically to prevent the recurrence of attacks.

An additional advantage of paredrine over ephedrine is the absence of any reactions caused by central nervous stimulation, such as nervousness, tremor, apprehension, or insomnia.

PRESSOR ACTION

Observations on the pressor action of paredrine are relatively meager. Alles[5] found that paredrine has a more intense pressor action than phenylisopropylamine (benzedrine). Abbott and Henry[7] reported that paredrine is about twice as effective as ephedrine in raising blood pressure in man. Altschule and Iglauer[8] concluded that paredrine was a more potent pressor drug than benzedrine, and found the compound of value as an adjunct in the treatment of the vasomotor collapse of hemorrhage, pulmonary embolism, and surgical shock.

In the present study, observations were made on fourteen subjects from the hospital wards. The measurements were made under basal conditions, in the postabsorptive state, with the subject in the recumbent position. Repeated observations were made under similar conditions. After several control blood pressure readings and pulse rate determinations, paredrine hydrobromide was administered. After a subcutaneous dose, usually of 20 mg., subsequent blood pressure readings were made at five, fifteen, thirty, forty-five, and sixty minutes. After an oral dose, readings were taken after fifteen, thirty, sixty, and ninety minutes. Fourteen subjects received the drug subcutaneously in 20 mg. doses. In nine instances, the compound was given by mouth in 40 mg. doses and in four cases in 80 mg. doses. Table II shows the average rise in arterial pressure, the maximum effect, and the duration of action.

TABLE II

THE RESPONSE OF THE BLOOD PRESSURE TO VARYING DOSES OF PAREDRINE IN NORMAL SUBJECTS

DOSE	AVERAGE RISE SYSTOLIC AND DIASTOLIC (MM. HG)	MAXIMUM RISE SYSTOLIC AND DIASTOLIC (MM. HG)	DURATION (MIN.)
20 mg. subcutaneously (14 cases)	51/16	73/30	40- 75
40 mg. by mouth (9 cases)	52/17	106/42	60-120
80 mg. by mouth (3 cases)	69/24	82/33	120

In every case a sustained pressor effect was obtained. After oral administration this effect was noted within fifteen minutes in most instances, and the maximum effect occurred in thirty to sixty minutes. The duration of the pressor action after a dose of 40 mg. was sixty to ninety minutes, and, with the 80 mg. dose, one and one-half to two

hours. After the subcutaneous injection of 20 mg. the onset of action was within five to ten minutes, and the maximum effect occurred usually within fifteen to thirty minutes. The blood pressure returned to normal in most cases within an hour. The diastolic pressure was only slightly affected, as compared with the systolic pressure, but in no case was a lowering of diastolic pressure observed. There was also a marked variation in the intensity of the effect in different persons.

COMPARISON OF EFFECTS OF ORAL AND SUBCUTANEOUS ADMINISTRATION

One of the features which limits the usefulness of epinephrine is its instability and inactivity on oral administration. This applies to most of the sympathomimetic amines. In fact, the introduction of ephedrine was a great advance largely because it permitted the oral use of a sympathomimetic amine. In previous studies on cardiac standstill by one of us (M. H. N.), it was found that other hydroxyamines, such as tyramine, hordenine, synephrin, and neosynephrin, were ineffective on oral administration.[4] In the present study it was found that paredrine retained a surprising degree of activity when administered by mouth. The following illustrates the comparative effectiveness by oral and subcutaneous administration:

TABLE III

AVERAGE BLOOD PRESSURE RISE

ORAL, 40 MG. (9 CASES)		SUBCUTANEOUS, 20 MG. (14 CASES)	
Systolic	52 mm.	Systolic	51 mm.
Diastolic	17 mm.	Diastolic	16 mm.

These observations indicate a complete or practically complete absorption and utilization of paredrine when it is administered by mouth. In one of the nine subjects to whom the drug was given by both routes, a relatively slight pressor effect was noted on oral administration as compared with the reaction after subcutaneous injection. This had been observed previously in the studies on cardiac standstill. In one case of heart block, 100 mg. by mouth failed to influence the ventricular rate or raise the arterial pressure. There is apparently an occasional case in which the drug is destroyed in the gastrointestinal tract, or there is incomplete absorption. A similar variation in activity has been observed after the oral administration of ephedrine.[9] It is important to recognize this variation in activity for, in some instances, an effect may be obtained by increasing the average oral dose of 40 mg.; occasionally, the relative inactivity on oral administration makes the drug unsuitable for use by this route.

COMPARISON OF PAREDRINE AND PAREDRINOL (VERITOL)

Paredrinol, the N-methyl derivative of paredrine, has received a great deal of attention in the German literature under the name

"Veritol."[10] A number of publications have appeared on the human and animal pharmacology of the drug, and it is claimed that this compound is a superior remedy in the treatment of circulatory collapse of various types. It is reported that the pressor action is mainly due to the emptying of venous stores of blood, and it has been suggested that the drug differs from other sympathomimetic amines which produce an increase in arterial pressure mainly by peripheral vasoconstriction. There is some difference of opinion as to the mode of action, and some question whether this compound differs fundamentally from certain other substances of this group.[11] In this country, Stead and Kunkel[12] concluded that the pressor action of paredrinol was due to one or both of the following mechanisms: (1) a direct vasoconstrictor effect on small blood vessels, and (2) a primary increase in venous tone, causing an increased venous return to the heart and a secondary rise in arterial pressure. In a recent study, paredrine and paredrinol were administered to a group of fifteen normal subjects subcutaneously and by mouth.[13] In every instance paredrine produced a much greater pressor effect. Also, by either route of administration, the duration of the effect was definitely longer after giving paredrine (Table IV).

TABLE IV

MAXIMUM RISE IN BLOOD PRESSURE (IN MM. OF HG) AFTER EQUIVALENT DOSES OF PAREDRINE AND PAREDRINOL IN FIVE NORMAL SUBJECTS

		SUBCUTANEOUSLY, 20 MG.		ORALLY, 40 MG.	
		SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC
1	Paredrine	18	3	32	12
	Paredrinol	9	2	14	8
2	Paredrine	36	6	57	12
	Paredrinol	22	2	58	6
3	Paredrine	54	8	90	19
	Paredrinol	20	1	14	0
4	Paredrine	52	22	46	14
	Paredrinol	22	6	46	0
5	Paredrine			96	17
	Paredrinol			66	24

EFFECT OF PAREDRINE ON BLOOD VOLUME

Recently, observations have been carried out on the effect of paredrine on blood volume.[12] It has been claimed that continuous administration of epinephrine causes a reduction in blood volume and a condition resembling shock.[15] Since paredrine has a prolonged sympathomimetic action, it seemed important to ascertain the effect of the drug on blood concentration and blood volume. The specific gravity of the blood was ascertained in six normal subjects by the Barbour and Hamilton falling drop method[16] before the administration of the drug and at the height of the pressor effect. In no instance was any significant alteration in the specific gravity observed. In three cases the "Evans Blue" dye

method was used in the estimation of blood volume after the method described by Gibson and Evans.[17] The dye concentration in the plasma was estimated with a photoelectric cell colorimeter. In each instance two control readings of dye concentration were made during the half hour preceding the administration of the drug. Readings were again made ten minutes after administering paredrine, at the height, and also at the end of the pressor effect. There was no significant deviation in the blood volume or any significant change in hematocrit readings after the administration of the drug.

PRESSOR EFFECT IN SPINAL ANESTHESIA

Various pressor substances have been used to counteract or prevent the fall in blood pressure which frequently accompanies spinal anesthesia. Epinephrine, ephedrine, neosynephrin, and benzedrine have been used for this purpose. Altschule and Gilman[18] employed paredrine in fifty patients who developed a rapid and marked fall in blood pressure during spinal anesthesia. In every case the administration of paredrine was followed by a return of the blood pressure to a satisfactory level. In the present study,* observations were made on 114 patients who received spinal anesthesia. The drug was administered intramuscularly preliminary to the spinal tap, so that an interval of three to five minutes elapsed between the time the paredrine was given and the actual subdural injection of the anesthetic. Procaine hydrochloride was the anesthetic used in most cases. In eighteen, the operations were on the upper abdomen, and, in ninety-six, the surgical procedure was on the lower abdomen, prostate, rectum, or lower extremities. Fifty per cent of the patients were over 50 years of age. In ninety-five patients, or 83 per cent, the response could be described as satisfactory, in that a single pre-anesthetic injection of paredrine maintained a satisfactory blood pressure level throughout the operation. Of these, twenty-one received 10 mg., seventeen received 15 mg., and the remaining fifty-seven received 20 mg. of the drug. In eleven patients, or 10 per cent, the response could be considered as excessive, for a single pre-anesthetic injection elevated the blood pressure 50 mm. or more above the pre-anesthesia level. Two of these patients complained of severe headache. Two patients in this group received 10 mg. of the drug, and the remaining nine received 20 mg. In eight patients, or 7 per cent, a definite fall in blood pressure occurred during the operation. A second injection of paredrine promptly raised the blood pressure to a satisfactory level in each case, and this level was maintained throughout the operation (Table V).

After the experience with this group, the following method seemed satisfactory: a dose of 10 to 15 mg. of paredrine for low operations, and 20 mg. for operations on the upper abdomen. In an additional

*These observations were carried out by Dr. Julius Hersh, of the Department of Anesthesia, Cedars of Lebanon Hospital.

250 cases a satisfactory blood pressure level was maintained, and a second injection of paredrine was not necessary in any case. As compared with ephedrine, which had been used previously, it was found that a more satisfactory blood pressure level could be maintained more consistently, and that there were definitely fewer hypotensive reactions. In addition, paredrine proved much more efficient in restoring the blood pressure when it fell to a critically low level during spinal anesthesia.

TABLE V

THE PRESSOR ACTION OF PAREDRINE IN EIGHT PATIENTS WHO SHOWED A DEFINITE FALL IN BLOOD PRESSURE DURING SPINAL ANESTHESIA

OPERATION	BLOOD PRESSURE BEFORE ANESTHESIA	PAREDRINE MG. PRE-SPINAL (MG.)	BLOOD PRESSURE CHANGE DURING ANESTHESIA	PAREDRINE MG. DURING ANESTHESIA (MG.)	BLOOD PRESSURE AFTER PAREDRINE
Colostomy	160/110	20	190/120-80/60	10	120/80
Gastrectomy	110/82	20	140/ 90-80/40	10	160/70
Resection of colon	150/100	15	150/100-80/50	20	120/80
Transurethral resection	130/70	15	120/ 60-84/60	10	120/84
Cystotomy	158/112	20	120/ 90-80/70	20	150/100
Abdominal prostatectomy	145/84	10	160/ 80-80/60	20	140/80
Emergency cystotomy	50/40	20	120/ 80-50/40	10	100/80
Laparotomy for bowel obstruction	160/110	15	150/100-60/40	20	140/80

HEART RATE

Fourteen subjects received a subcutaneous injection of 20 mg.; the heart rate was increased in five (average, 11 beats per minute) and decreased in seven (average, 7 beats per minute). In two cases the rate was unchanged. Nine subjects received 40 mg. by mouth; there was an increase in the heart rate in three (average, 9 beats per minute) and in three there was no change. Four subjects received 80 mg. by mouth; the rate was decreased in three (average, 5 beats a minute) and unchanged in the other. It is usually stated that administration of the sympathomimetic amines is followed by a slowing of the heart rate, and that this relative bradycardia results from reflexes arising in the aorta and carotid sinus caused by the elevated blood pressure. However, Blumgart[19] found an average increase of 16 beats a minute in eight of ten subjects after a subcutaneous injection of 0.5 c.c. of a 1:1,000 solution of epinephrine. Starr and his associates[20] noted, in six subjects who were carefully observed, a 21 per cent increase in pulse rate after the administration of 0.7 c.c. of a 1:1,000 solution of epinephrine and a 9.7 per cent increase in rate after ephedrine. Altschule and Iglauer[8] observed a decrease in pulse rate after paredrine in three subjects and no change in two. Epinephrine increased the heart rate in the two cases which were studied. Keys and Violante[21] observed, after the administration of neosynephrin, a definite bradycardia which lasted thirty

to ninety minutes, with pulse rates varying from 30 to 45 per minute. They concluded that the drug produces a primary bradycardia which is relatively independent of pressor reflexes over the vagus nerve. These observations indicate that the sympathomimetic amines may have a variable effect on the heart rate. It would appear that paredrine stands between epinephrine and neosynephrin; it causes less cardiac acceleration than the former, and less inhibition than the latter.

DISCUSSION

Since the isolation of epinephrine, in 1901, several hundred chemically related compounds have been synthesized and studied. However, only two substances, ephinephrine and ephedrine, have been widely used in therapeutics. Before the use of a new drug is suggested, it must be demonstrated that the drug has some advantages over the older compounds. Paredrine has a more sustained action than epinephrine, and its especial advantage is that it can be administered by mouth. As compared with ephedrine, paredrine is definitely more potent and is free of the unpleasant side actions which result from cerebral stimulation. As regards the effect on cardiac standstill, our observations indicate that all three compounds act in a similar manner; they have the property of increasing the activity of lower rhythmic centers, thus preventing cardiac arrest. The therapeutic indication is in conditions in which cardiac asystole may occur. In cases of heart block in which syncopal attacks are frequent, ephinephrine is the drug of choice. In those instances in which attacks are infrequent, a drug which is effective on oral administration is desirable. Paredrine in doses of 40 to 60 mg. three times a day will usually increase ventricular rhythmicity, so that the tendency to standstill is lessened. The same therapy is indicated in patients who have syncopal attacks associated with a hypersensitive carotid sinus.

As regards the pressor action of epinephrine and paredrine, there is evidence that there are differences in their mode of action, i.e., there is not only a quantitative but also a qualitative difference in their effects. Altschule and Iglauer[8] found that the pressor action of paredrine was not associated with any increase in cardiac output, whereas there was a striking increase in cardiac output after epinephrine. These observers also noted a marked increase in the velocity of blood flow after epinephrine, but this did not occur after paredrine. Epinephrine usually lowers the diastolic pressure, whereas paredrine raises it. After the pressor response to epinephrine there is usually a hypotensive phase. This diphasic effect has not been observed with paredrine. Epinephrine constricts the minute vessels of the skin. Our observations indicate that paredrine dilates the small vessels of the skin. After an intradermal injection of paredrine we have noted a flushing of the skin, with an increase in skin temperature, whereas epinephrine always produces a zone of intense pallor. We have observed this difference when the drugs

are given subcutaneously. A flush of the skin, especially of the face, is noted often after the administration of paredrine, in contrast with the pallor observed after epinephrine.

It has been claimed that prolonged administration of epinephrine can reduce blood volume. No change in blood volume or specific gravity has been observed during the pressor action of paredrine.

These differences in mode of action are important in the application of pressor substances to therapy. In spite of the powerful action of epinephrine, its pressor action has found little practical application in therapeutics. In the most important hypotensive state, that of peripheral circulatory collapse, it is usually stated that epinephrine and related compounds are of no benefit and may be harmful. However, there is some difference of opinion on this point. Best and Solandt[22] found that histamine shock, traumatic shock with hemorrhage, and traumatic shock respond favorably to treatment with a pressor substance and concentrated serum. Kabat and Freedman[23] reported experiments in which the slow administration of epinephrine maintained the blood pressure during and after intestinal manipulation, and observed an increase of 300 per cent in the survival rate. Favorable results have been reported in shock by the administration of ephedrine, neosynephrin, and paredrinol. Kunkel, et al.,[24] noted that paredrinol had a beneficial effect in the collapse which may be induced by sodium nitrite. We have observed symptomatic relief in orthostatic hypotension with a combination of benzedrine and paredrine. This has also been noted by Korns and Randall.[25] Stead and Ebert[26] found paredrinol useful in the treatment of circulatory collapse resulting from hemorrhage. It must be concluded that the exact status of the pressor substances in shock is not entirely settled. In surgical or traumatic shock these drugs should be considered only as adjuncts in treatment, but there is evidence that they may be of benefit in association with other measures. It should be pointed out that the differences in the action of epinephrine and paredrine would favor the latter drug in the treatment of shock. The more sustained effect of paredrine, the nonparticipation of the heart in the pressor action, the absence of any change in blood volume, and the dilating effect on the minute vessels of the skin are features which make this drug more applicable. In addition to the effects during spinal anesthesia, we have observed a definite and sustained rise in blood pressure, with clinical improvement, in circulatory collapse associated with a variety of conditions. Altschule and Iglauer[8] found that, with paredrine, they could restore the blood pressure to normal in Addison's disease and in shock caused by coronary thrombosis. They state also that the drug is a useful adjunct in collapse associated with hemorrhage, pulmonary embolism, and surgical shock. Although these observations are encouraging, the exact value of paredrine in shock must await the study of a large group of patients in shock, with observations on the circulatory dynamics before and after the administration of the drug.

CONCLUSIONS

Paredrine is a potent epinephrine-like compound which has a prolonged action and is effective on oral administration.

Paredrine is the most effective orally active compound in the prevention and treatment of cardiac standstill.

Paredrine produces a definite and sustained rise in arterial pressure.

The evidence available indicates certain differences in the mechanism of the pressor action of paredrine and epinephrine.

Paredrine is effective in the maintenance of satisfactory blood pressure levels during spinal anesthesia.

Although more data are essential, the drug appears to be of value in certain types of shock.

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DISCUSSION

DR. J. MURRAY STEELE, New York, N. Y.—I became interested in paredrine by the back door, so to speak, during a study of carotid sinus sensitivity. In the literature, and again today, the fact that there is no obvious central action of this drug was referred to. In attempting to sort out the varieties of carotid sinus sensitivity, that which is supposed to be cerebral in origin is quite regularly stopped—the convulsions are stopped—by the administration of paredrine, although they are not stopped by atropine.

I would like to ask Dr. Nathanson on what grounds evidence rests to the effect that there is no central action of this drug.

DR. S. P. SCHWARTZ, New York, N. Y.—I should like to ask Dr. Nathanson what effects the sympathomimetic drugs have upon the carotid sinus itself.

Secondly, I wonder if Dr. Nathanson could tell us how epinephrine hydrochloride is absorbed after its parenteral administration during standstill of the ventricles.

DR. WALLACE M. YATER, Washington, D. C.—Will Dr. Nathanson tell us whether maintenance of administration can be carried on and what the maintenance dose might be in the average case?

DR. IRVING S. WRIGHT, New York, N. Y.—Dr. Nathanson said that apparently in some instances the drug is not utilizable by mouth, whereas in other instances it is. I should like to ask him whether any studies have been made as to whether the drug is better utilized in an acid or alkaline medium, and, if so, whether he has found any comparison between in vitro and in vivo studies in that regard.

DR. CARL A. JOHNSON, Chicago.—These drugs, known as sympathomimetic drugs, may have both sympathetic and parasympathetic actions. This is especially true of neosynephrin HCl, for if 10 mg. are given subcutaneously to the unanesthetized human subject, a marked slowing of the heart rate results, which probably is a parasympathetic effect, and there is an increased peripheral vascular constriction from the sympathetic effect. Although these drugs are similar in chemical structure, their actions differ qualitatively and quantitatively.

I would like to ask Dr. Nathanson about the site of action of paredrine, just as the previous discussers have. Both ephedrine and epinephrine increase the irritability of the heart, and death from toxic doses is caused by ventricular fibrillation. Neosynephrin HCl, however, does not increase the irritability of the heart, and animals which die from toxic doses do not have ventricular fibrillation. In view of these differences in the action of these drugs on the heart, I would like to know whether paredrine increases the irritability of the heart, and also what the cause of death is when animals receive lethal doses.

As far as neosynephrin HCl is concerned, I take exception to the statement that this drug is not active when given by mouth. If large enough doses are given by

mouth on an empty stomach, a hemodynamic effect results, but the dose necessary to effect this is often in the toxic range (200 to 400 mg.). The dosage that produces this effect varies from patient to patient, and even in the same person. The oral use of this drug, therefore, is not practical.

DR. NORMAN E. FREEMAN, Philadelphia.—We have used paredrine hydrobromide in studies on the circulation in traumatic shock, and, in contradistinction to adrenalin, the pressor effects seem to be greater than the peripheral arterial constrictor effects. That may be one of the reasons why the administration of paredrine does not cause hemoconcentration and other evidences of reduced blood volume.

Kunkel, Stead, and Weiss, in their studies on paredrine, arrived at the conclusion that its effect was chiefly to produce constriction of the larger blood vessels, especially on the venous side, which would tend to mobilize the available blood volume. Experience in the treatment of low blood pressure from spinal anesthesia, and the low blood pressure which is associated with sudden interruption of vasoconstrictor impulses during the course of thoracolumbar sympathectomy would bear out these ideas.

I would like again to ask Dr. Nathanson what he thinks about its action on the various components of the vascular system, not only the heart, but also the great vessels.

DR. MORRIS H. NATHANSON.—I am glad to have these questions, for several of them were taken up in the portion of the paper that I did not have time to read.

In answer to the question whether paredrine possesses a central stimulating action, resembling that of benzedrine or ephedrine, I can definitely say that the drug has no such action in therapeutic doses. I have seen no such effect in any case; also, recently, it has been reported from Tainter's laboratory that the threshold dose for the central stimulating action in animals for benzedrine is 0.3 mg. per kilogram; for ephedrine, 5 mg. per kilogram; and for paredrine, 80 mg. per kilogram.

In answer to the question as to how the drug can be absorbed during cardiac standstill, the drug was not administered during the standstill. The procedure was to make a record showing the cardiac arrest. The drug to be tested was then administered, and, after suitable intervals, the carotid sinus pressure was repeated to ascertain whether the cardiac standstill could still be induced.

As to the question whether the presence or absence of gastric acidity may explain the variation in activity when it is given by mouth, I have no definite data on this point. I suspect that this is not the explanation. On the whole, the drug is well utilized when administered by mouth, but there is the occasional person who shows little effect after oral administration.

Dr. Johnson brought up several interesting points. As regards the parasympathetic effects of these compounds, the bradycardia caused by neosynephrin may be considered as such an effect, although I do not believe that this has been definitely demonstrated. Our studies on the effect on the heart rate would place paredrine between epinephrine and neosynephrin; the drug has less of a cardiac accelerating action than epinephrine, and also produces less cardiac inhibition than neosynephrin. As regards the effect of paredrine on the heart and blood vessels, I can see no evidence of any parasympathetic action.

I do not feel that the final answer on the mechanism of the pressor action can be given at this time. There is a rise in venous pressure, but it is doubtful whether the pressor effect is secondary to this action. The effect is probably chiefly one of arteriolar constriction. I feel from our studies that this statement is justified. My opinion is that the various sympathomimetic amines act alike in the prevention of cardiac standstill. The difference is only a quantitative one, and some are more effective than others. As regards the pressor action and the effect on the blood

vessels, there is not only a quantitative difference, but also a qualitative difference, especially between epinephrine and certain other substances of this group. For example, epinephrine, in its pressor action, increases cardiac output, accelerates blood flow, and produces pallor of the skin by constricting the small vessels. Paredrine apparently does not increase cardiac output or cause acceleration of blood flow. The effect on the blood vessels of the skin is entirely different. An intradermal injection of epinephrine produces pallor, with reduction of temperature, whereas a similar injection of paredrine causes redness and warmth around the site of injection. It is these and other differences which suggest that the objections to the use of epinephrine in shock may not apply to other sympathomimetic amines.

ISOLATED MYOCARDITIS

Otto Saphir, M.D.
Chicago, Ill.

MYOCARDITIS, in general, is a rarely observed clinical entity which, as White[1] stated, can be diagnosed by the realization of myocardial involvement in infectious diseases, or, in a few cases, circumstantially by the discovery of acute heart block, abnormal electrocardiograms, etc. Christian[2] recently stressed that myocarditis, in the sense of an acute inflammatory process, is rare and of minor clinical importance. However, he continued, "if by acute myocarditis is meant the circulatory disturbances with or without evidence of degeneration of the muscle fibers or cellular infiltration between them, associated with infectious diseases, it is a frequent occurrence." It thus seems clear that the clinical concept of myocarditis is often linked with the physiologic disturbance in the circulatory apparatus, rather than with anatomically demonstrable inflammatory changes in the myocardium. One reason for this discrepancy lies in the fact that there is very little information obtainable for a correlation between anatomic changes in the myocardium and a clinical diagnosis of myocarditis. This may be explained in part by the fact that, during routine autopsies, as a rule only a few blocks are cut from the myocardium. The absence of inflammatory changes in these few sections certainly does not preclude a diagnosis of myocarditis, and a consequent report of a normal or degenerated myocardium often misleads the clinician, who expected a positive diagnosis to confirm his observations. That the diagnosis of myocarditis has fallen into discredit is, therefore, often definitely the fault of the pathologist who has failed to examine more representative blocks.

From a recent comprehensive review of the literature on myocarditis,[3] it is apparent that actual myocardial inflammatory changes in the various diseases are not rarely described. Often, however, these changes are not mentioned in the diagnosis and only very rarely is myocarditis diagnosed clinically. Excepted from such a general conclusion is myocarditis in rheumatic fever, which, because of the characteristic microscopic picture, is often diagnosed anatomically and certainly often considered clinically. Also, paradoxically enough, in view of the fact that, as many pathologists believe, syphilitic myocarditis—in the absence of miliary gumma—cannot be recognized anatomically, so-called syphilitic myocarditis is often diagnosed clinically.

From the Department of Pathology, Michael Reese Hospital, Chicago.
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There is a type of myocarditis—isolated, or Fiedler's[4] myocarditis—which, during the last decade, has received increased attention simply because it is more or less diffuse and thus easily recognized anatomically, even when only a few sections are examined. Although this type of myocarditis seems relatively rare, it is interesting that, since attention was drawn to it in 1929,[5] a number of reports have appeared in the literature, whereas until that time the condition was apparently little known in this country. More recent reports indicate that, if the clinician and pathologist alike are aware of this condition, not only the pathologist but also the clinician diagnoses the disease correctly. Therefore, it would seem likely that, from a review of the clinical and anatomic pictures of isolated myocarditis, some data concerning myocarditis in general might be forthcoming.

Fiedler's, or isolated, myocarditis is a special form of myocarditis, although it is not specific in the anatomic sense. Although Fiedler[4] termed this myocarditis "acute interstitial," it is clear—as Šikl[6] pointed out—that Schmorl, who studied the hearts in Fiedler's cases microscopically, actually described parenchymatous changes in some of the hearts, with outspoken necrosis. From a review of the reported instances, it appears that this type of myocarditis denotes more or less diffuse inflammatory changes in the myocardium, of wide variety and varied etiology; the principal thing that they have in common is isolated involvement of the myocardium by a nonspecific lesion, without inflammatory changes in the endo- and pericardium. Thus, rare instances of rheumatic myocarditis (Kramár[7]), in which there are Aschoff bodies without accompanying endo- or pericarditis, do not fall within the category of isolated myocarditis, nor are cases of pyemia with abscesses in the myocardium (suppurative myocarditis) included. There are also records of patients who died of heart failure, and, at autopsy, showed not only diffuse myocarditis, but also granulomas with necrosis and giant cells. Although some of these granulomas at first suggest a syphilitic or tuberculous etiology, neither tubercle bacilli nor spirochetes are present; however, sometimes there is a positive history of tuberculosis or of a syphilitic infection. This is referred to as granulomatous or productive myocarditis. But in the absence of any causative agents, if syphilis and tuberculosis can be ruled out, these granulomatous lesions may also be classified with "isolated myocarditis." Although extensive necrosis is not mentioned in many of the case reports of "isolated myocarditis" (Karsner[8]), the isolated involvement of the myocardium and the unknown origin would lead to the inclusion of this myocarditis as a subvariety of the isolated form.

There are other recorded instances of isolated myocarditis in which there were inflammatory cells, many of which were eosinophiles. The belief is expressed that this type of myocarditis may be of an allergic nature, perhaps resulting from a special idiosyncrasy to either bismuth

or arsenic compounds, although adrenalin has also been held responsible (Franz[9]). However, since only the myocardium is involved, with no changes in the endo- or pericardium, and since the other organs show no characteristic change, it seems wise to include these myocarditides also under isolated myocarditis, especially since the allergic nature of this lesion has not been proved.

Inasmuch as we were aware of the existence of isolated myocarditis and realized the importance of examining many blocks of the heart muscle in order to make a correct diagnosis, we routinely and carefully studied the myocardium in all cases in which the possibility of myocarditis was suggested, principally by evaluation of the autopsy observations, but also post hoc by certain clinical observations. As has been pointed out elsewhere, few data are available concerning the frequency of myocarditis in general autopsy material, and there is no information regarding the incidence of isolated myocarditis. Chudějová[10] (1933), in reviewing autopsy material in 8,474 cases, mentioned 221 instances of myocarditis. However, since no details were given, it seems that certain instances of arteriosclerotic heart disease must have been included among the 221 hearts. Brown and Hunt[11] studied 113 instances of infectious diseases and found myocarditis in forty-six.

In 5,626 autopsy cases, routine examination of the hearts disclosed 240 instances of myocarditis. Not included in this material are contagious diseases and syphilis. Isolated myocarditis of the granulomatous variety, as discussed above, was encountered only once, and diffuse myocarditis fourteen times.

The following are some of the clinical data on thirteen patients, and a summary of the gross and histologic observations, showing inflammatory changes isolated in the myocardium. An analysis of these and other reported cases is presented with a view to clarifying this entity. The possible causes of isolated myocarditis are also discussed.

CLINICAL NOTES*

Since none of the patients was observed by the author, the most essential facts given here were taken from the clinical records. There were twelve instances of the diffuse type, with no circumscribed granulomatous lesions, and one which was characterized by the formation of granulomas. The twelve instances of myocarditis, although anatomically principally identical, may be classified as those in which neither clinically nor at autopsy were other lesions demonstrated which might be correlated with the myocarditis; and those in which other diseases were present, but, as far as could be ascertained, were not likely to have borne any causative relation to the myocarditis. Five of the twelve patients with the diffuse type of myocarditis had other diseases. One had Laennec's cirrhosis, and another, tuberculous osteomyelitis. Two other

*I am indebted to the members of the Department of Medicine of Michael Reese Hospital for the records of these patients.

patients died suddenly after an operation for ventral hernia and for carcinoma of the large intestine, respectively. A fifth patient had a nodular colloid goiter with toxic symptoms and died suddenly before a contemplated operation. Seven patients at autopsy showed no disease except the myocarditis. Only one of these seven patients gave a history of a "septic sore throat." None of the patients had been treated with either adrenalin or any arsenic compound.

The patient with granulomatous lesions in the myocardium died suddenly without a history even suggesting disease.

The ages of the twelve patients with diffuse myocarditis varied from 10 months to 55 years. There were eight males and four females. The clinical diagnosis of heart disease was made in only three cases, and myocarditis was not recognized in a single instance. The heart disease was diagnosed as pericarditis, coronary thrombosis, and mitral stenosis with insufficiency, respectively. On two of these three patients electrocardiograms were made, and the following changes were encountered (Dr. L. N. Katz): The first had a rate of 67 per minute. The P-R interval was 0.44 sec. QRS was upright in Lead I, inverted in Leads II and III, and slurred or notched in the limb leads, and the duration was prolonged to 0.16 sec. P was upright in Leads I and II and diphasic in Lead III. S-T_1 was depressed, and S-T_2 and S-T_3 were elevated. T_1 was inverted, and T_2 and T_3 were upright. The chest lead (Lead CF_2) showed that QRS was prolonged, almost entirely electronegative, and notched and small, with the first phase inverted; S-T was normal in contour, and the P wave was diphasic. Interpretation: Sinus rhythm, first degree A-V block, intraventricular block of the common type. A definitely abnormal record.

The electrocardiogram in the second case showed a ventricular rate which averaged 96. No P waves were seen; instead, there were oscillations in the isoelectric portion of the record which were irregular in spacing, amplitude, and contour (best seen in Lead I) and had a rate which averaged about 340 per minute. The QRS was tiny in the limb leads, and definitely notched and prolonged; its duration was 0.12 sec. S-T was isoelectric in Lead I and depressed slightly in Leads II and III. T was tiny in the limb leads, inverted in Lead III, upright in Lead I, and indiscernible in Lead II. In Lead III a bizarre, premature, ventricular complex was seen. The chest lead (CF_2) showed that QRS was almost entirely negative, S-T abnormally elevated, and T upright; at times there was an upright U wave. Interpretation: Fine auricular fibrillation, with a moderately rapid ventricular rate; a ventricular premature systole; intraventricular block of the indeterminate ("low voltage") type. A definitely abnormal record. Note: Toward the end of Lead I artifacts are present, causing instability of the base line.

In one of the cases in which heart disease was recognized clinically the heart was enlarged and a rough systolic murmur was heard over the

apex. Three days before death, evidence of cardiac failure was noted. The second patient was admitted with epigastric distress and was orthopneic and cyanotic. The heart dullness was diffusely enlarged, and there was a pulsus paradoxus. The cardiac borders did not shift with change of position. The clinical diagnosis was pericarditis. The third patient had had shortness of breath for some time. He was dyspneic and had palpitation. The apex beat was diffuse, and a systolic thrill was noted over the apex and over the pulmonic area. All these patients had in common a weak, rapid pulse and low arterial blood pressure. One had precordial pain. However, the progressive myocardial failure dominated the clinical picture.

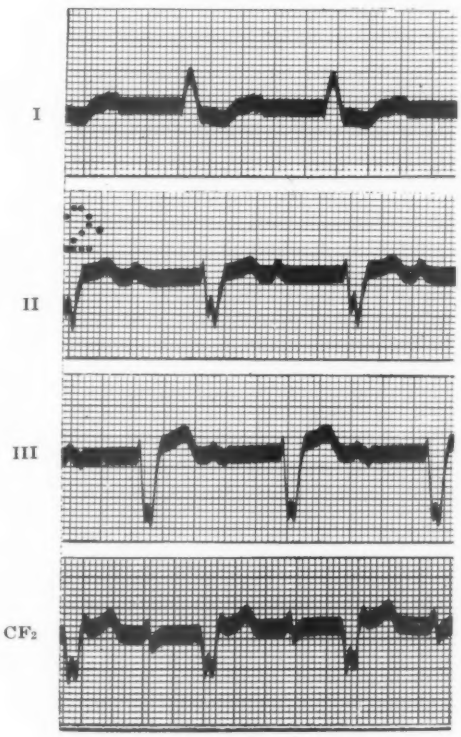

Fig. 1.

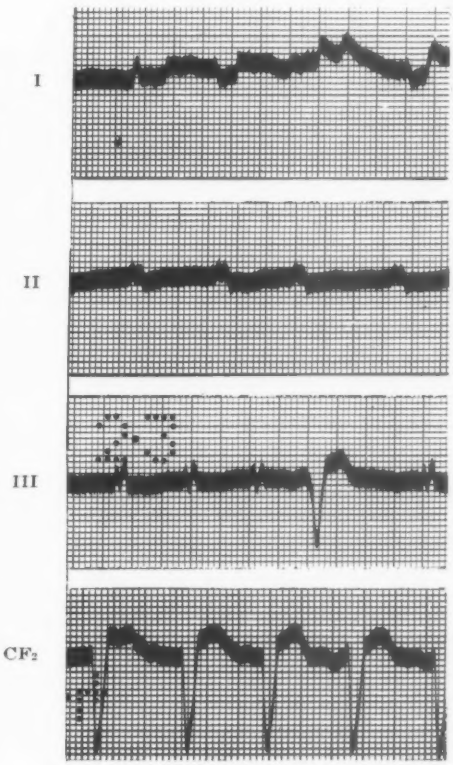

Fig. 2.

Nine of the twelve patients with diffuse myocarditis died suddenly. In one case death was attributed to coronary thrombosis. Two patients died unexpectedly after laparotomies. Three patients were brought to the hospital in extremis, were very cyanotic, and died before any history could be taken.

The patient who had granulomatous myocarditis, a 40-year-old man, had, as far as could be ascertained, never complained of any illness, but suddenly dropped dead while working.

ANATOMIC OBSERVATIONS

All of the hearts were enlarged and dilated. Neither the pericardium nor the endocardium showed any abnormalities. The myocardium was pale gray, and often faintly tinged with yellow, with minute grayish streaks or larger areas of gray and white which varied, but corresponded roughly to the relative age of the disease. Histologically, the lesions were diffuse and principally interstitial in location, although the heart muscle fibers were also involved. There were neither characteristic cellular accumulations nor did one particular type of cell predominate.

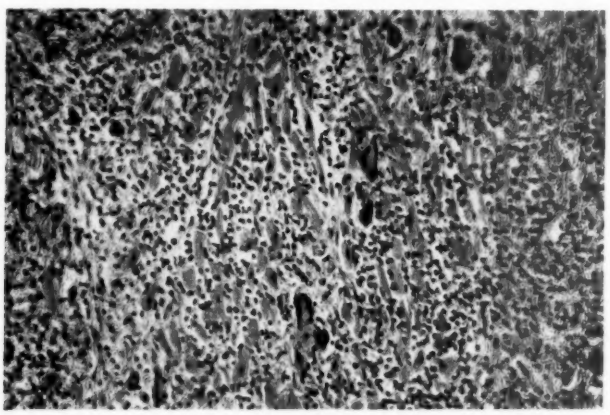

Fig. 3.—Granulomatous myocarditis. Note the giant cells, most of which are muscle giant cells. Hemotoxylin eosin preparation, ×130.

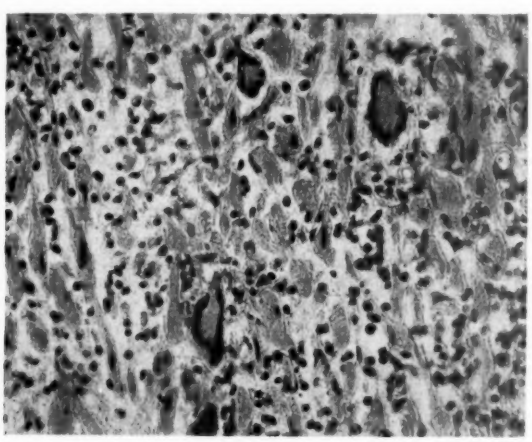

Fig. 4.—Granulomatous myocarditis. Note the muscle giant cells. Hemotoxylin eosin preparation, ×280.

Lymphocytes and endothelial leucocytes were the most commonly encountered cells, although polymorphonuclear leucocytes and eosinophilic leucocytes were also seen. Mast cells, which are normally found within

the interstitial tissue of the myocardium, seemed more numerous than usual. Transitions from the inflammatory cellular exudate to scar tissue were often encountered. Although often a perivascular distribution of the inflammatory cells was conspicuous, these accumulations never resembled those of rheumatic myocarditis.

The hearts of the three patients in whom heart disease had been recognized clinically showed many recent and old fibrotic lesions throughout the myocardium. Also present, however, were accumulations of lymphocytes and endothelial leucocytes.

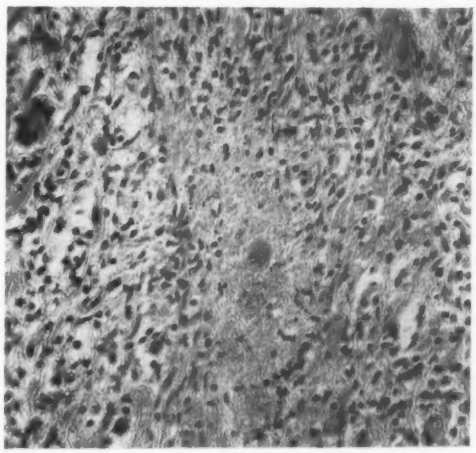

Fig. 5.—Granulomatous myocarditis. Note the central area of necrosis. Hemotoxylin eosin preparation, ×200.

The heart which was the seat of the granulomatous myocarditis was about normal in size. Throughout the myocardium there were many irregular, yellowish-white areas, about 3 mm. in diameter, occasionally somewhat larger, which showed a tendency toward fusion. In places they reached the endocardium and there assumed the form of minute nodules. The pericardium showed no change. Histologically, there were large areas of necrosis, at the periphery of which many lymphocytes, eosinophilic leucocytes, and a few endothelial leucocytes were encountered, but none of these cells predominated particularly. Conspicuous were a number of giant cells, with nuclear distribution more or less toward the periphery. Some of these giant cells were definitely not muscle giant cells, but resembled those seen in tuberculosis. In addition, however, many typical muscle giant cells were also encountered. Circumscribed areas without necrosis, consisting of lymphocytes, eosinophilic leucocytes, and a few giant cells, were numerous. These regions were richly vascularized, and the vessels had thin walls. The adjacent myocardium disclosed a diffuse infiltration predominately of eosinophilic leucocytes and lymphocytes. Neither spirochetes nor tubercle bacilli could be demonstrated.

COMMENT

From the data presented, it is clear that a form of myocarditis exists which is unaccompanied by either endocardial or pericardial lesions, and that it occurs in the absence of acute infectious diseases which are known occasionally to cause myocarditis. In ten of thirteen of these patients sudden death was attributed to the myocardial changes.

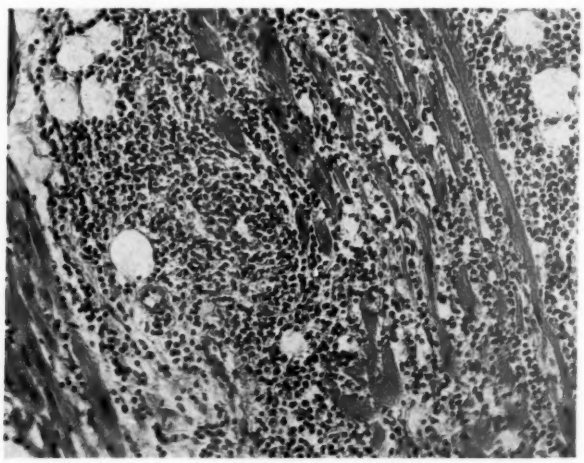

Fig. 6.—Diffuse myocarditis. Most of the inflammatory cells are lymphocytes. A few polymorphonuclear leucocytes are also present. Hemotoxylin eosin preparation, ×150.

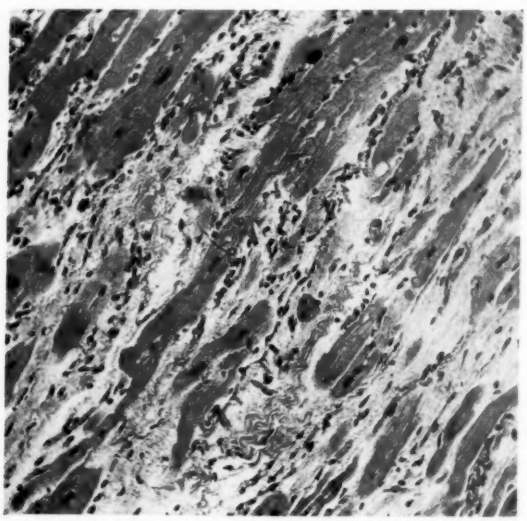

Fig. 7.—Old myocarditis. Note the fibrosis and the inflammatory cells. Hemotoxylin eosin preparation, ×250.

Diffuse myocarditis may easily be subdivided into the acute, fulminating form, which rapidly causes cyanosis and death, and a more protracted form. A subdivision has been made by Boikan,[12] who stated that

acute myocarditis, although it usually caused the death of the patient, might occasionally undergo healing, with much formation of new connective tissue. The patients in this series who died suddenly after surgical procedures, as stated above, and the three who were brought to the hospital in extremis apparently belong to this first group. The second group includes the truly chronic forms which invariably cause death after several months. The left ventricle, particularly, and occasionally also the left auricle, are involved in these instances. The initial changes, according to Boikan,[12] are round cell infiltrations; the cells either localize in groups, or more diffusely infiltrate the interstitial tissues. The capillaries are conspicuously dilated. He stated that, later, eosinophilic leucocytes are seen, and the muscle fibers become necrotic. Granulation tissue is formed gradually, and eventually foci of fibrosis replace the destroyed muscle fibers. The three patients in whom, as mentioned before, heart disease was diagnosed clinically, apparently belong to this group. The third group (Boikan[12]) is characterized by the simultaneous presence of recent and old inflammatory changes. Simon and Wolpaw[13] reported such an instance. Because this is a progressive disease which culminates invariably in the death of the patient, with the clinical picture of progressive cardiac failure, the term "pernicious" was applied by Boikan.[12]

Progressive heart failure and rather sudden symptoms of congestive failure are often present in these cases. Simon and Wolpaw[13] stressed progressive heart failure in their patient. Bailey and Andersen[14] remarked on their patient's cardiac pain. Cyanosis, sometimes intermittent, is occasionally observed. It should again be emphasized that the diagnosis of myocarditis is rarely, if ever, made; the scant signs are misinterpreted as evidence of either coronary disease or pericarditis. Mitral disease is also an occasional premortem diagnosis. In children with symptoms referable to heart disease, toxic myocardial degeneration is most frequently diagnosed. An overlooked infection, possibly diphtheria, was suggested as a cause of myocarditis by Singer.[15] The clinician is seemingly under a spell which prevents him from diagnosing myocarditis.

Changes are also reported in the electrocardiogram. De la Chapelle and Graef[16] were apparently the first to find evidence of severe impairment of conduction in this disease.

Death from isolated myocarditis often occurs suddenly. In this series ten patients succumbed unexpectedly. The patients in Major and Wahl's[17] series, who also probably fall in this group, died suddenly. Helwig and Wilhelmy[18] stressed that interstitial (isolated) myocarditis should receive serious consideration in any case of sudden and unexpected death in which, at autopsy, naked eye examination reveals no anatomic lesion which could be held responsible.

The cause of isolated myocarditis is obscure; many possible factors have been considered, such as upper respiratory infections, "influenza,"

toxemias, and injuries of the myocardium brought about by such chemicals as sparteine and adrenaline. Recently, Chamberlain[19] reported a patient with a history of alcoholism. It must also be emphasized that neither grossly nor histologically does isolated myocarditis vary in any essential from the myocarditis which is seen occasionally in the course of pneumonia and other acute infectious diseases, and in other conditions. Gouley, McMillan, and Bellet[20] described peculiar myocardial changes in pregnancy, but did not wish to imply that this form of myocardial change is specifically dependent upon pregnancy or on the puerperal state, because they had encountered it at least twice in men. They remarked that the clinical picture and the gross morbid anatomic changes in these cases were similar in many respects to those of Fiedler's myocarditis. Thus, the question arises whether or not one is justified in segregating Fiedler's myocarditis—perhaps excluding the granulomatous form—as a special type of myocarditis. The classification would not be based on the gross or histologic picture, but rather on clinical observations, absence of definitely known causes of myocarditis, and subsequent autopsy observations in those cases in which the clinical diagnosis was not made.

Isolated myocarditis also occurs in infancy and childhood. Two infants are included in Smith and Stephens'[21] series. Lindberg,[22] Blühdorn,[23] Maslow and Lederer,[24] Greenebaum, Felson, and Zeligs,[25] and Kenny and Sanes[26] reported relevant instances. It is interesting to note that Singer,[15] who found myocarditis in two infants who died suddenly, suggested that it might have been caused by a clinically overlooked infection, possibly diphtheria. In our series three instances were found in children; they were 10 months, 15 months, and 3 years old, respectively.

The granulomatous form of isolated myocarditis is much more rare than the diffuse type. Again it may be emphasized that neither tubercle bacilli nor spirochetes can be demonstrated in these hearts, although a history of either tuberculosis or syphilis may be obtained (Taussig and Oppenheimer[27]). However, in this respect mention may be made of Karsner,[8] who stated that syphilis cannot be excluded because of a negative Wassermann reaction and the inability to demonstrate spirochetes. Earlier reports of this kind of myocarditis were made by Baumgartner,[28] Saltykow,[29] and Gierke,[30] and, more recently, Magner,[31] Šikl[6] (who reviewed the literature), Hansmann and Schenken,[32] Jonas,[33] and Miller[34] reported relevant instances. In discussing Miller's case, Lillie[35] remarked that, in experimental tularemia, a granulomatous myocarditis which resembles the lesion in human granulomatous myocarditis is not infrequently found. This is interesting because the question immediately arises whether or not there may be other infectious diseases that also produce granulomatous lesions in which the causative organism cannot be demonstrated, and in which the granulation tissue is not

characteristic enough to lead to the recognition of the etiologic agent. Blastomycosis can be ruled out because it is easy to recognize blastomyces in section. Sidorov[36] reported a case of granulomatous myocarditis caused by *Balantidium coli* and demonstrated the organism. However, trichinous myocarditis is one form which presents neither a characteristic nor pathognomonic histologic picture, and, apparently, trichinae are not found in the myocardium of the experimental rabbit later than eight days after the infection. Although in exceptional instances the larvae were found on the twenty-sixth and twenty-ninth day of the infection, they are, as a rule, not present in the myocardium, for patients usually die between the fourth and sixth week of the infection.

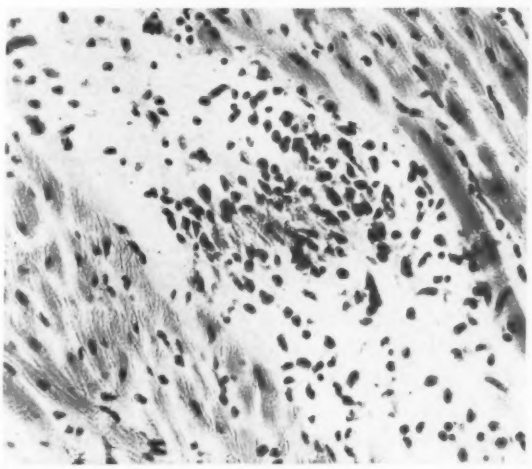

Fig. 5.—Trichinous myocarditis. Note the granulomatous lesion, with necrotic foci. The patient died in the fifth week of the disease. *Trichinella spiralis* was found in the diaphragm. Iron hemotoxylin eosin, ×300.

Histologically, the myocardium shows focal or diffuse infiltrations of neutrophilic leucocytes, lymphocytes, and a few mononuclear leucocytes and plasma cells. Usually many eosinophilic leucocytes are also present, although their absence is occasionally stressed, whereas, in isolated (Fiedler's) myocarditis, a predominance of eosinophiles is sometimes noted (Magner[31]). The muscle fibers are degenerated or actually necrotic. Since it is now known that the larvae are present in the heart, as a rule, only shortly after the infection, their absence does not preclude a diagnosis of trichinous myocarditis. In a personal observation, actual, small, granulomatous lesions were found in the myocardium in a case in which *Trichinella spiralis* was encountered in the diaphragm. Histologically, the changes in the myocardium resembled those which are seen in granulomatous myocarditis and in diffuse isolated myocarditis. Only the discovery of trichinae in the diaphragm prevented us from classifying this myocarditis among the isolated forms. Weller[37] also remarked on the similarity of these two conditions, and Libman[38] ques-

tioned the similarity of eosinophilic and isolated myocarditis, as reported by Smith and Stephens.[21] Thus, it seems clear that if attention is focused on the heart only, not only trichinous myocarditis, but perhaps also other types, may well be confused with isolated myocarditis. On the other hand, the question must be raised whether or not, in some instances, isolated, particularly granulomatous, myocarditis may be the result of one of the known causes of inflammation.

There are instances on record (Rosenthal[39]) of myocardial inflammation in which only on histologic examination were valvular changes demonstrable. Thus, it is evident that such cases do not fall within the category of isolated myocarditis, and the absence of valvular lesions must be confirmed by microscopic examination before a definite diagnosis, based on myocardial changes, can be made.

Rheumatic fever as the causative agent can be ruled out. There are instances on record of rheumatic myocarditis without endocardial or valvular involvement, but the lesions in rheumatic myocarditis are characteristic enough morphologically to rule out rheumatic fever as the etiologic agent. Although it has been suggested (Sacks[40]) that diffuse infiltration of the myocardium may represent an exaggeration of the less conspicuous leucocytic collections which accompany the Aschoff body, this does not seem to be a likely explanation of the cellular infiltrations in isolated myocarditis.

In some instances of myocarditis the inflammation was diffuse, involving large fields, and in others, many small foci of subacute inflammation were present. It is more likely that the difference in such cases lies in the severity of the myocarditis, rather than that it constitutes a different type of myocarditis. The three types of myocarditis described by Boikan[12] are probably different stages of the same disease.

Lindberg's[22] report of isolated myocarditis is noteworthy because of his suggestion that the initial changes may be of the serous myocarditis type, similar to those found by Wenckebach[41] in the beriberi heart, and described by Rössle[42] and Eppinger, Kaunitz, and Popper.[43] The serous exudate in this type of myocarditis stimulates connective tissue overgrowth, and myocarditis, with marked fibrosis, ensues. The myocarditis described by Lindberg,[22] and also by Boikan,[12] may perhaps have shown a "serous" component in its intitial stage. It is interesting that Eppinger, Kaunitz, and Popper[43] mentioned burns as possible causes of serous inflammation, and that there are reported cases of isolated myocarditis in which burns are suggested as the possible etiologic agent (Zuppinger,[44] and Kaufmann[45]).

Lately there has been more and more discussion whether or not the myocarditis may be of an allergic nature, perhaps a result of a special idiosyncrasy to certain chemicals (bismuth, arsenic compounds, neosalvarsan, etc.). Šikl,[6] Ueke,[46] Nelson,[47] Zalka,[48] and Brown and McNamara[49] reported such instances (see also Saphir[3]). Maxwell and

Barrett's[50] patient had a severe dermatitis, apparently caused by sulphur ointment. Bernheim-Karrer's[51] patient (a 13½-month-old child) had severe eczema of unknown origin. Brown and McNamara[49] stated that "in the light of our present knowledge, therefore, the acceptance of the allergy hypothesis to explain the myocardial lesions of arsphenamine dermatitis rests on the exclusion of other causes on morphologic grounds and on the compatibility of the lesions with those encountered in other types of known allergy." Franz[9] suggested that the myocardial lesion which he had observed may have been the result of the administration of adrenalin, or possibly was caused by hypersensitivity toward adrenalin. French and Weller[52] very recently described an interstitial myocarditis, with many eosinophilic cells, in the hearts of 126 patients whose sole common factor was that one or more of the sulfonamide drugs had been administered shortly before death.

These observations are interesting, but sufficient data are not available to permit any definite conclusion in regard to the origin of isolated myocarditis. Many more examples should be studied, not only for myocardial changes, but, in addition, complete autopsies, with careful microscopic examination of all organs, are essential to ascertain whether or not pertinent changes may be encountered in other organs, particularly muscles, liver, kidneys, and brain.

Isolated myocarditis is also described in cases of hyperthyroidism. One of the patients here mentioned, who showed evidence of hyperthyroidism, died suddenly before a contemplated thyroidectomy could be performed. Magner's[31] patient, although he showed no symptoms of hyperthyroidism, died eighteen hours after subtotal thyroidectomy. However, in a study of the relation between thyroid disease and myocardial changes, it was concluded[3] from the evidence on hand and from a review of the literature that there are no consistent inflammatory changes in the myocardiums of patients who died of hyperthyroidism.

SUMMARY

There is a type of myocarditis of unknown origin which is not accompanied by endo- or pericarditis. It occurs in patients who have no other disease that may be correlated with the myocarditis. This myocarditis may also be present in apparently healthy persons who, more or less suddenly, develop progressive myocardial weakness and succumb quickly. Clinically, the outstanding manifestations, in addition to the progressive myocardial failure, are a weak, rapid pulse, low arterial pressure, and an increase in the area of cardiac dullness. Precordial pain may be present. The disease occurs at any age, although young people seem more frequently affected. Therefore, arteriosclerotic heart disease can easily be ruled out. There is no history of rheumatic fever. The patients often die suddenly. Of thirteen patients in this series, ten succumbed suddenly. It seems that clinicians, for some reason, rarely, if ever, diagnose the myocarditis.

Anatomically, isolated myocarditis does not vary in histologic details from the myocarditis which is occasionally encountered in the course of acute infectious disease. A diffuse and a granulomatous type can be distinguished. The latter is much rarer, and morphologically somewhat resembles the granulomas of tuberculosis and syphilis. Histologically, many giant cells (muscle giant cells) are often recognized. The minute granulomas which are seen in trichinous myocarditis may also occur in isolated myocarditis. Although nothing is known as to the cause of either the diffuse or granulomatous form, it seems imperative in every instance to examine histologically other organs and structures besides the heart in pursuit of the causative agent, as in trichinosis, or, perhaps, tularemia. Lately, a hypersensitivity, particularly to arsenic compounds (arsphenamine and salvarsan), has also been regarded as responsible.

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A NOTE UPON MORE ACCURATE MEASUREMENT OF DIASTOLIC BLOOD PRESSURE

J. Marion Read, M.D., and J. Sewall Brown, M.D.
San Francisco, Calif.

THE auscultatory method of measuring blood pressure has almost entirely replaced all other methods. The reason for the rapid and universal adoption of Korotkow's auscultatory method was that it furnished a means of measuring diastolic pressure, which could not be done by palpation.

THE ERROR IN MEASURING DIASTOLIC PRESSURE

Numerous studies have been made upon the reliability of blood pressure measurements, and the subject has recently been reinvestigated and summarized by Shock and Ogden.[1] A review of most of the published figures reveals that the probable error in measuring diastolic pressure is greater than it is in measuring systolic pressure. This arises apparently from two causes, as follows:

1. The systolic pressure, as measured by the auscultatory method, is subject to check by palpation, and although it usually reads four to ten points higher by the former method, nevertheless palpation furnishes a means of checking the accuracy of the systolic reading which is not available in measuring diastolic pressure. Observation reveals that this fact is too often forgotten, or neglected, by clinicians, although its usefulness was stressed many years ago by Kilgore[2] and others, and reemphasized in the "Standard Method for Taking and Recording Blood Pressure Readings" adopted by the American Heart Association and the Cardiac Society of Great Britain and Ireland.[3]

2. Great uncertainty seems to exist regarding the point at which diastolic pressure should be read. Some believe that it should be read at the end of the third phase (change of sound), and others at the end of the fourth phase (disappearance of sound). Some life insurance companies ask for a recording of both these end points, and some mention a fifth phase. The committee of the American Heart Association which drew up the "Standards"[3] recognized the difficulties, and also provided for two readings when the end points are not identical. This seems unnecessary, and the stand of Wakerlin[4] upon this point is well taken because there can be only one diastolic pressure, and there are

From the Department of Medicine, Stanford University Service, San Francisco Hospital, Dept. of Public Health of the City and County of San Francisco.
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means of establishing this, as we will show, by utilizing other available means of reading the end point rather than relying solely upon auscultation.

A MEANS OF REDUCING THE ERROR

It is common knowledge that, throughout the range of pulse pressure, there is a definite oscillation of the mercury column, or of the needle of an aneroid instrument. As the pressure in the encircling cuff is increased, oscillation begins as soon as this pressure against the artery just exceeds the intra-arterial pressure at the end of diastole. The entrance of each pulse wave into the compressed segment of artery makes a sound, and it also increases the intra-arterial pressure, which is transmitted back through the compressing system into the indicator. This causes an intermittent oscillation which is usually about 1 mm. Hg at the diastolic (and systolic) end points.

Attention to these two points of change in amplitude of the movement of the indicator will convince anyone that they correspond to the same points at which the systolic and diastolic pressures are read by auscultation. In fact, it is possible to measure systolic and diastolic blood pressure with considerable accuracy by utilizing only this visual method.

EXPERIMENTAL TESTS OF THE METHOD

To ascertain the degree of accuracy attainable by this method, one of us (J. M. R.) recorded diastolic and systolic pressure by the visual method alone, and the other (J. S. B.) took the pressure by auscultation. The readings were made simultaneously upon 102 ward patients, omitting only those with cardiac irregularities. We used alternately a mercury and aneroid sphygmomanometer. The degree of correspondence between the auscultatory and visual (oscillometric) methods is shown in Table I.

TABLE I

FREQUENCY OF OBSERVED DIFFERENCES BETWEEN BLOOD PRESSURE MEASUREMENTS BY THE VISUAL AND BY THE AUSCULTATORY METHOD

DIFFERENCE (MM. HG)	0	2	4	6	8	10	12 TO 14	16 TO 18	20 AND ABOVE	NO. OF OBSERVATIONS
Diastolic	15	26	20	20	6	4	7	2	2	102
Systolic	28	15	12	19	10	5	6	6	1	102

In addition to the above means of showing the close correspondence between the results of the two methods of measuring blood pressure, we calculated, also, the coefficients of correlation for the two series of observations. For diastolic pressure the correlation coefficient was 0.95, and for systolic pressure it was 0.98. Since the coefficient of 1.0 indicates perfect correlation, these are extremely, almost unbelievably, high values. We therefore hasten to point out that, as with other statistical measures, certain factors influence them which are not evi-

dent in the measures themselves. In this case the very high correlation coefficients resulted partly from the great range of our data. The diastolic pressures ranged from 30 to 140, and the systolic, from 72 to 250 mm. of mercury. Very close agreement at both extremes of the diastolic and systolic series tended to raise the correlation coefficient materially. Also, it was observed, when tabulating the observations in order to calculate the correlation coefficient, that the scatter about the regression line was small (especially for systolic pressures), and, furthermore, that those which were read too high were balanced by an almost equal number that were read too low. This factor was very potent in raising the coefficients of correlation to the high figures obtained in this series of observations.

THE GREATER VARIABILITY IN READING DIASTOLIC PRESSURE

The amount of "scatter," or variability in a series of observations, can be expressed by the statistical measure known as the *standard deviation*. This measure was calculated for our data, and for the diastolic pressure readings gave values of 4.92 and 4.8 by the auscultatory and visual methods, respectively. The standard deviations for the systolic pressure readings were lower, namely, 4.33 for the auscultatory, and 3.96 for the visual, method.

We believe that the lower coefficient of correlation and the larger standard deviations for diastolic pressure are significant and constitute additional proof of the greater difficulty in measuring diastolic pressure. This point was further investigated by calculating the standard deviations for several series of blood pressure measurements.

The first is the published series of Wright, Schneider, and Ungerleider.[5] In 1938, "to emphasize the need for a universal standardization of the methods used in the measurement of blood pressure," these investigators studied the blood pressure readings made by interns, postgraduate students, and attending physicians upon unselected patients at the New York Post-Graduate Hospital. The greatest variations were found in the readings of the postgraduate group; the least, in those of the attending physicians; and the interns' were intermediate. We calculated the standard deviations of the variations from the mean diastolic and systolic pressures for all three groups, sixty-eight observations in all. The standard deviation for diastolic pressure was 2.49, whereas it was only 2.1 for systolic pressure.

The second series of blood pressure readings (285 in number) was gathered in the past three years from three successive classes in physical diagnosis at the Stanford University Medical School. After being taught the technique of taking blood pressures, each member of a small student group took the pressure of a patient, or another member of the group, and recorded it independently. This was done with the subject lying, and then standing, so that each student had two opportunities

to measure each subject's pressure. The instructor (J. M. R.) also took and recorded the subject's blood pressure, and the average systolic and diastolic pressures were ascertained. The standard deviations from these means, in millimeters of mercury, when calculated for both pressures, were 3.94 for the diastolic and 3.05 for the systolic pressure.

This greater variability in reading diastolic pressure is also shown by the figures of Shock and Ogden,[1] which were obtained by having two observers listen through the same stethoscope. Hamilton, Woodbury, and Harper[6] published figures which show that, in comparing the direct (cannula) with the indirect (sphygmomanometer) method, the diastolic readings obtained by the indirect method deviated more from the values obtained directly than did the systolic measurements.

DISCUSSION

All of the foregoing observations indicate clearly that diastolic pressure presents greater difficulties in measurement than does systolic pressure. Recognition of this fact prompted Smith[7] to write: "The criteria for measuring diastolic pressure have been (and still are) variable among individuals and countries" (he probably had in mind the matter discussed in the third paragraph of this paper). He was discussing the reasons why life insurance companies do not require blood pressure readings for all applicants. Although the value of these data to the insurance companies was not minimized, he pointed out that an inaccurate measurement of the pressure was likely to be more misleading than none at all. It is not only true that "blood pressure is the third most important routine physiologic measurement that the modern physician uses with a fine degree of precision"[8] (sic), but it is also true that it is the only quantitative measure of a physiologic function upon which life expectancy can be estimated by insurance companies.

Clinically, it is usually of little consequence if the blood pressure is not measured accurately, even when there is an error of 10 mm. Hg. This obviously is not true with respect to life insurance examinations, as all examiners and medical directors realize. Inability or failure to measure the pressure accurately is a matter of considerable monetary consideration to the companies, and of economic and social import to the applicant. In other fields the accurate measurement of blood pressure can become crucial, e.g., when it is required as part of a physical examination preliminary to acceptance for employment in either private or civil positions; most pertinent just now is its inclusion as part of the examination of selectees under the Selective Service Act of 1940. With upper limits of 90 and 150 for diastolic and systolic pressures, respectively, the mode of life of a young man for the next year or two may hang upon a few millimeters of mercury, depending on how his pressure is read by the examiner. No one's blood pressure is constant, but, nevertheless, an examiner should be able to measure it accurately

within 4 to 6 mm. That this does not seem to be the case was shown by Wright, et al.,[5] in their study of the results obtained by groups of physicians who measured the pressure simultaneously. Their results, which could have been anticipated, are nevertheless a startling record of inability to obtain even approximate values in one of the most frequent clinical procedures.

In view, therefore, of this demonstrably greater difficulty in accurately reading the diastolic end point, it seems desirable to sharpen the auditory estimate of this point by the visual impression gained from noting the change in amplitude of oscillation of the indicator at the diastolic (and systolic) end points. In fact, it has been our experience that the blood pressure of certain persons is almost impossible to measure by auscultation, so that it is necessary to resort to the visual and palpation method to furnish the end points.

CONCLUSIONS

There is need for more accurate measurement of diastolic and systolic pressure, particularly the former, which is more difficult to measure than the latter. Coordinating the change in amplitude of oscillation of the needle or mercury column with the change in sound makes for greater accuracy.

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ACUTE CORONARY THROMBOSIS IN INDUSTRY

II. Indirect Injuries From Toxic Gases and Other Physical Agents

Harry D. Leinoff, M.D.
New York, N. Y.

THE medical-legal importance of acute coronary occlusion in industry was discussed in a previous paper.[1] This study is concerned particularly with the reaction of the heart to indirect injuries caused by exposure to toxic fumes, electricity, infections, and foreign proteins.

The patients were workers (except Case 6) who applied for compensation benefits, believing that certain incidents which had occurred because of, and during the course of, employment had caused acute heart disease. The most common diagnosis was acute coronary occlusion, although a better diagnostic term would have been acute toxic myocarditis or coronary circulation insufficiency. These clinical impressions rested on a varying combination of first recorded medical observations, a careful history, the examination, the subsequent clinical course, and the electrocardiographic, roentgenographic, and laboratory findings.

It can be safely stated that in all injuries the amount of damage is usually in direct proportion to the offending force and that the physical status of an organ determines its response to trauma.

CASE REPORTS

Case 1.—F. G., a 65-year-old porter, was found unconscious, having been overcome by fumes escaping from a leaking gas heater. He was given first aid and was put to bed, but he refused hospitalization. The diagnosis was acute monoxide poisoning. He complained of severe headaches, nausea, vomiting, and weakness. The following day a pulse arrhythmia and falling blood pressure were noted, without cardiac complaints. These findings were significant in view of a known asymptomatic essential hypertension. He was seen five days later with no complaints. The heart was enlarged to the left; the sounds were distant and lacked snap; the pulse rate and rhythm were normal; there were no signs of decompensation; the blood pressure was 120/70; and the retinal arteries were moderately sclerotic. Serial electrocardiographic tracings showed sinus rhythm, left axis deviation, and acute myocardial damage. He remained symptom free except for transient heart pains and made a good functional recovery.

Comment.—This man was in good clinical health although he had a known essential hypertension with some coronary artery sclerosis.

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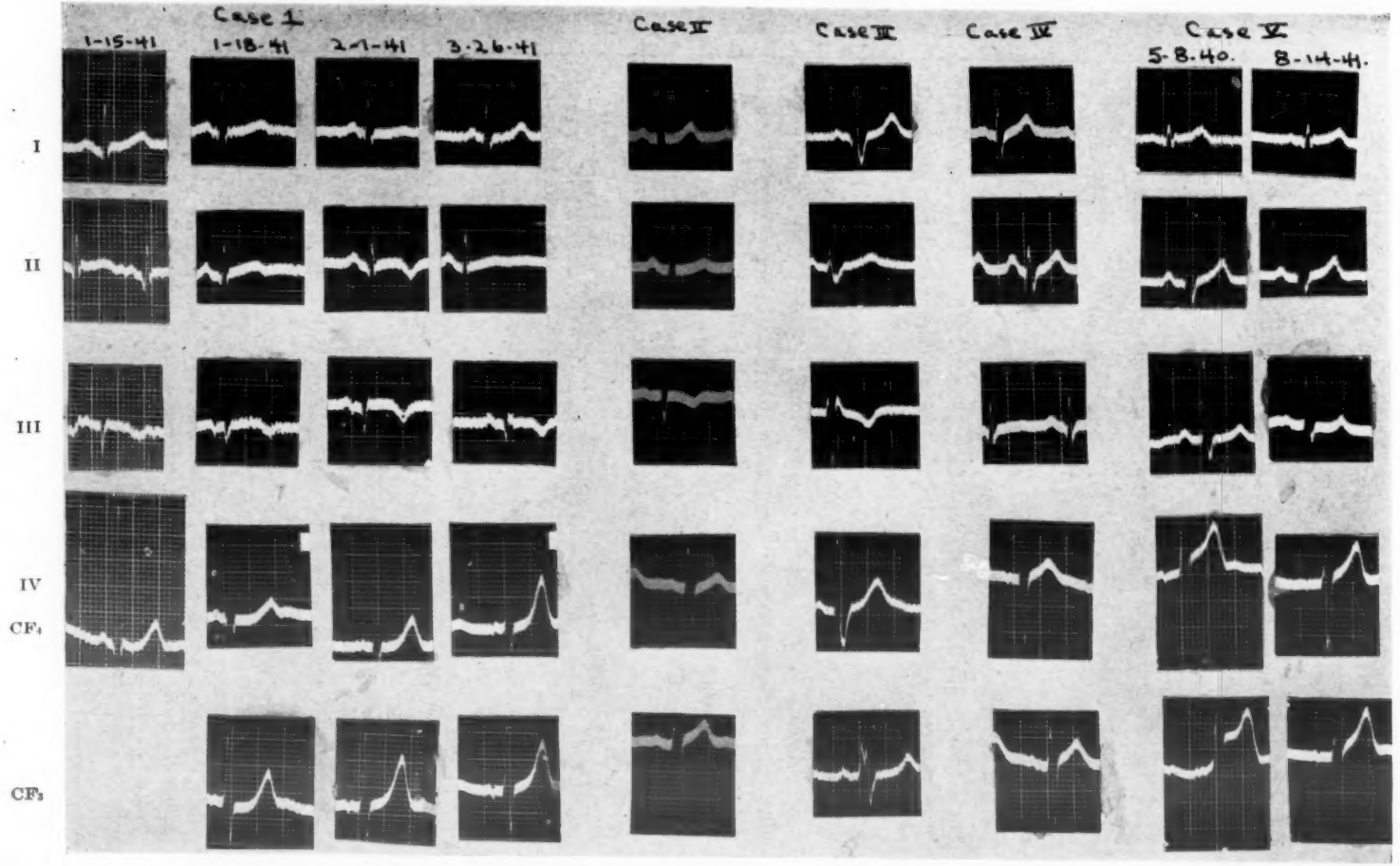

Fig. 1.—CF positions same as suggested by American Heart Association.

After exposure to illuminating gas, he became unconscious and developed typical objective signs of acute heart damage within twenty-four hours. This sclerotic heart was probably damaged by the large dose of carbon monoxide.

Carbon monoxide combines with blood hemoglobin to form carboxyhemoglobin, a stable compound which interferes with oxygen absorption; this produces a relative asphyxia, thus placing an excessive demand on the heart.[2-7] If this oxygen want is persistent, functional and organic changes may follow. In sclerotic and potentially diseased hearts more lasting and extensive damage may result. Drinker[2] and Beck[3, 4] believe that an exposure to this gas may precipitate clinical disease. This case would tend to support this view. Many observers feel that, in addition to the anoxemia, this gas can produce an acute or subacute myocarditis with round cell infiltration,[2-4, 6, 7] a lesion which has been demonstrated in experimental animals[3, 4] and at autopsy.[6, 7] In conclusion, it can be stated that carbon monoxide gas in fairly large doses can damage the heart by producing a toxic myocarditis or an acute coronary circulation insufficiency secondary to the oxygen want or by direct action on the coronary vessels.

CASE 2.—J. C., a 46-year-old truck driver, was forced to drive seventeen hours with closed windows during a bad spell of winter weather. At the end of this period, he became dizzy, felt a tightness across the chest, and had a severe headache. He stopped the car, opened the door, and lost consciousness. He was hospitalized with a clinical diagnosis of acute carbon monoxide poisoning, although no laboratory tests were performed to confirm this impression. While in the hospital he complained of precordial distress; rapid heart action and exertional dyspnea appeared when he was allowed to get up. The past history was normal. The patient did hard physical work without any difficulty on one job for eleven years.

He was seen seven months later with the same cardiac complaints. The heart was enlarged to the left; the sounds were of poor quality; the blood pressure was 130/100; the pulse rate and rhythm were normal; the response to exercise was poor; and the retinal arteries were moderately sclerotic. The electrocardiographic diagnosis was sinus rhythm, left axis deviation, myocardial damage, and possible posterior coronary occlusion.

Comment.—This man was in good clinical health until he was exposed for a long period of time to an atmosphere containing a moderate amount of carbon monoxide gas. This resulted in typical symptoms of poisoning with an acute cardiac crisis. The mechanistic possibilities are the same as in the previous case except for the slow cumulative effect of a moderate concentration of the gas. The automobile engine is a very common source of this poison. Gettler and Mattice[8] demonstrated that taxi drivers under ordinary working conditions may have as much as 6 per cent carboxyhemoglobin in the blood. There is little doubt that this patient absorbed a great deal of gas under the described working conditions.

Fig. 1.—CF positions same as suggested by American Heart Association.

CASE 3.—F. F., a 50-year-old automobile mechanic, was road-testing a car during a particularly cold spell with the windows closed. The floor boards had been removed, and gas fumes were seeping into the driver's compartment. At the end of an hour, he felt nauseous, faint, and dizzy and had a severe headache. He rested, but when he resumed his work, the same symptoms returned with a sense of chest pressure and rapid heart action. He was put to bed for ten days with a diagnosis of acute carbon monoxide poisoning; this was not confirmed by blood tests. On returning to work, he noticed that any contact with carbon monoxide resulted in cardiac symptoms which gradually became so bad that he was hospitalized. The past history was normal.

He was seen nine months later, complaining of exertional dyspnea and pain. The heart was normal in size, shape, position, movements, rate, and rhythm. The sounds were of poor quality and distant; a short systolic murmur was present; the blood pressure was 150/100; and the retinal arteries were moderately sclerotic. The response to exercise was poor. The electrocardiographic diagnosis was sinus rhythm, myocardial damage, and intraventricular heart block.

Comment.—F. F. was in good clinical health until he was exposed to a large dose of gas. Symptoms of monoxide poisoning and heart trouble resulted. He probably had an underlying sclerosis with silent myocardial changes, and this incident changed his clinical status.

CASE 4.—A. L., a 43-year-old laborer, attempted to remove two men who had been overcome by gas fumes while digging at the bottom of a deep shaft. In performing this task, he became faint, weak, and dizzy and lost consciousness. All three were finally removed by an emergency squad; the two workers died and only the patient survived. He was hospitalized with a diagnosis of acute "sewer" gas poisoning and myocardial damage. At this time he was unconscious and cyanotic and had a total cardiac arrhythmia which was considered auricular fibrillation, although no electrocardiograms were taken. He complained of rapid heart action, exertional dyspnea, precordial distress, severe headaches, nausea, vomiting, and abdominal pains. The past history was normal.

He was seen two and a half years later, complaining of weakness, exertional dyspnea, and cardiac pains. The heart was normal in size, shape, position, movements, rate, and rhythm. The sounds were muffled, and the blood pressure was 130/110. The electrocardiographic diagnosis was sinus rhythm, right axis deviation, and some myocardial damage.

Comment.—This man was in good clinical health until he was exposed to a mixture of gases which was toxic enough to kill two other men. He immediately presented cerebral and cardiovascular syndromes. This poison produced acute myocardial damage. The subsequent functional recovery did not parallel the objective findings, so that years later there were still complaints.

The offending substance was sewer gas, which is a combination of various hydrocarbons (such as methane), carbon dioxide, carbon monoxide, hydrogen sulfide, ammonia, nitrogen, and air. It is formed from decaying organic material and usually collects in pockets. The toxicity and symptomatology depends on the concentration of the various individual gases. These may replace the blood oxygen, causing asphyxia

with a resulting heart strain, or produce a toxic myocarditis. It is important to emphasize the toxicity of carbon dioxide, a substance which is usually considered nontoxic but which may be present in sewer gas in such high percentages as to be the lethal factor.

CASE 5.—W. R., a 21-year-old mechanic, stated that, while fixing an electric refrigerator, the sulfur dioxide tank exploded. He received chemical burns about the face, throat, mouth, and chest; local symptoms, cough, choking sensations, and a loss of taste and smell resulted. Several weeks later, exertional dyspnea, tachycardia, and weakness appeared. The past history was normal.

He was seen ten months later with the same cardiac symptoms. The heart and aorta were normal in size, shape, position, movements, rate, and rhythm. The sounds were of good quality; the blood pressure was 140/70; the response to exercise was normal; and the left cornea was scarred. The electrocardiographic diagnosis was sinus arrhythmia, no axis deviation, and some myocardial damage (precordial lead). Serial tracings subsequently were toward normal.

Comment.—This man was in good clinical health until exposed to a large dose of sulfur dioxide gas and liquid which caused severe local burns, exertional dyspnea, and tachycardia associated with changes in the electrocardiogram. The changes in the heart were of an acute nature and subsided with a good functional recovery.

Sulfur dioxide fumes irritate the respiratory mucous membranes, but when in contact with moisture change to sulfuric acid.[5, 7, 9, 10] In severe poisoning, a secondary anemia and asphyxia cyanosis may follow.[7, 10] The oxygen want is caused by either destruction of the oxygen absorbing membranes or the anemia which may follow. The anoxemia, if severe and prolonged, leads to structural and functional changes. The toxicity of sulfur dioxide gas, particularly as a refrigerant, was recently reviewed in an excellent study by McNally.[10]

CASE 6.—I. D., a 60-year-old housewife, was awakened from sleep by a severe attack of coughing, sneezing, difficulty in breathing, rapid heart action, and burning of the eyes and nose. This was caused by fumes escaping from a leaking sulfur dioxide tank in an electric refrigerator. She was kept in bed and subsequently complained of dyspnea and precordial distress. These symptoms had previously been present in a mild form, associated with a known hypertension.

She was seen about a month later with the same symptoms. The heart was enlarged to the left; the sounds had a fair quality with an accentuation of the second aortic; there was a rough systolic murmur; the retinal arteries were sclerotic; and the blood pressure was 250/110. The electrocardiographic diagnosis was sinus rhythm, left axis deviation, myocardial damage, and possible coronary occlusion. Serial tracings, which were not obtained, would have helped to determine whether the changes were old or new.

Comment.—This case was included because the toxin was sulfur dioxide gas, although of a nonindustrial origin. The objective findings were inconclusive, but the increase of symptoms were suggestive of an additional loss of function. The presence of an underlying sclerosis often alters the response of an organ to trauma and may dictate the subsequent clinical picture.

CASE 7.—C. M., a 48-year-old tool maker, stated that his work consisted of hardening instruments by heating them in a chemical bath at temperatures ranging from 1,800 to 2,000° F. This procedure resulted in varying amounts of sulfur dioxide, hydrogen sulfide, nitrous and minute amounts of cyanide fumes which were ordinarily led off by proper flues. Following the installation of a new set of ovens with in-

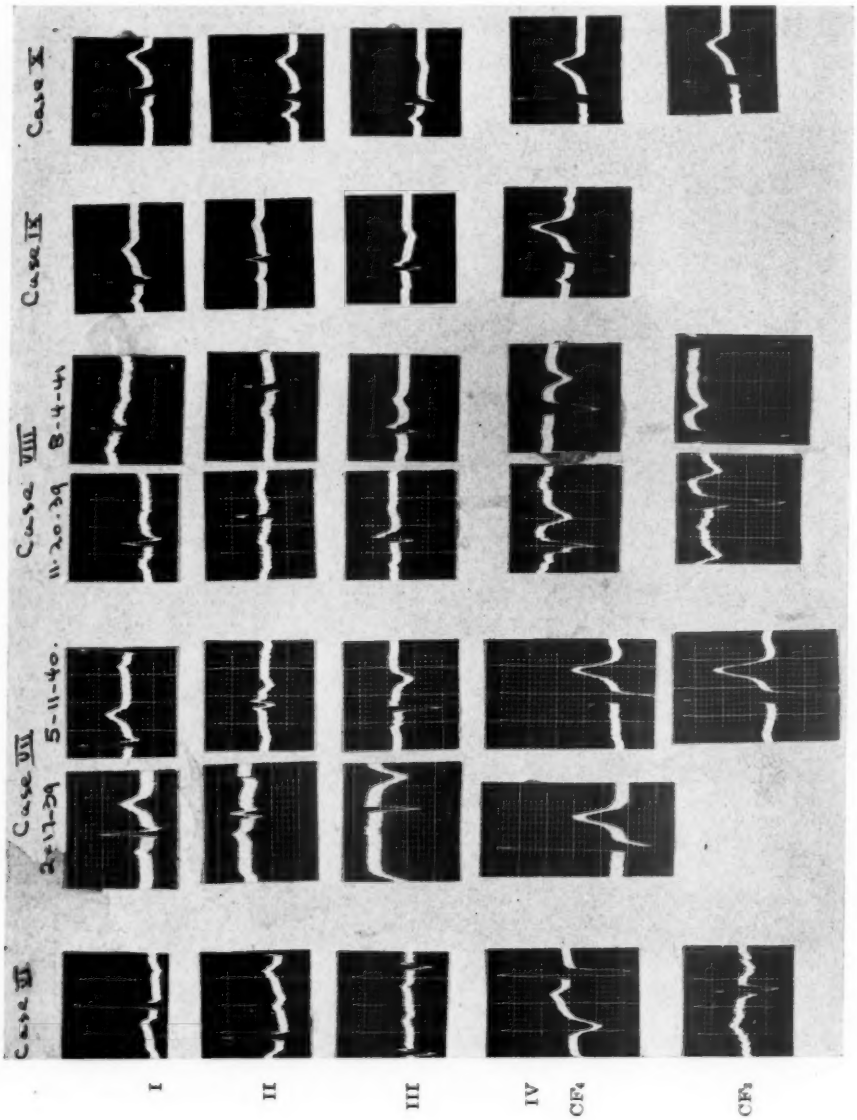

Fig. 2.

adequate ventilation, the patient developed nausea, headaches, dizziness, and rapid heart action. These symptoms recurred each time he used the furnaces, and on one occasion after ten hours of exposure he collapsed with a sense of pressure over the heart. He was put to bed with a diagnosis of acute coronary thrombosis. The past history was normal.

He was seen six months later, complaining of slight dyspnea. The heart was enlarged; the sounds were of fair quality; a soft apical systolic murmur was present; the blood pressure was 160/100; the response to exercise was normal; and the retinal arteries were moderately sclerotic. The electrocardiographic diagnosis was sinus rhythm, left axis deviation, myocardial damage, and residual signs of a posterior coronary occlusion.

Comment.—The patient began to have complaints after the installation of a new set of furnaces with improper ventilation. These symptoms were persistent, and following an unusually long exposure he had a cardiac breakdown. This may have been a coincidence, but, in view of the fact that some of these gases can affect the structure and function of the heart, it seems probable that this contact under adverse conditions may have played an etiologic role in a heart already weakened by sclerosis.

CASE 8.—S. B., a 45-year-old stevedore, punctured his left arm with a cargo hook. The laceration was sutured; an injection of tetanus antitoxin was given; and he was sent home. Within twenty minutes he was aware of extremely rapid heart action and felt weak, dizzy, and chilly. These symptoms persisted; dyspnea developed and in six hours became so bad that he was put to bed with a diagnosis of an acute coronary occlusion. Four days later he developed joint pains, and a diffuse rash appeared. The acute picture gradually subsided. The past history was normal.

He was seen four months later, complaining of exertional dyspnea, cardiac pains, choking spells, and weakness. The heart was enlarged to the left; the sounds were of poor quality; a systolic murmur was present; the blood pressure was 152/110; the response to exercise was poor; and the retinal arteries were moderately sclerotic. The electrocardiographic diagnosis was sinus rhythm, left axis deviation, myocardial damage, and anterior coronary occlusion.

Comment.—This man was in good clinical health until he lacerated his arm and received an injection of tetanus antitoxin. Within twenty minutes he developed signs of an allergic reaction with cardiac complaints, which in six hours warranted a diagnosis of occlusion. Was the heart collapse a mere coincidence, did the reaction to the foreign protein make an excessive demand on his sclerotic heart, or did the heart itself take place in the general allergic reaction. It is impossible to know the actual course of events, but cause and effect were too closely related to be considered an unqualified coincidence. A similar reaction following pneumococcus serum was recently reported.[11]

CASE 9.—S. A., a 46-year-old theatre manager, received a face scratch in a fight. This break of the skin became infected, and within forty-eight hours he developed typical signs and symptoms of erysipelas with a temperature of 104° F. On the fourth day, at the height of the infection, he complained of heart pain, cough, sore throat, and extreme difficulty in breathing. At this time the objective findings were cyanosis, dyspnea, tachycardia, poor heart sounds, and numerous basal râles. He made a gradual recovery. The past history was normal.

He was seen four months later complaining of moderate exertional dyspnea, precordial distress, weakness, and some ankle edema. The heart was enlarged to the left; the sounds were of poor quality; there was a slight pitting edema; the re-

sponse to exercise was poor; and the blood pressure was 104/80. The electrocardiographic diagnosis was sinus rhythm, left axis deviation, myocardial damage, and digitalis therapy.

Comment.—This man developed erysipelas, and at the peak of the infection signs and symptoms of an acute cardiac breakdown with decompensation appeared. This was caused by an acute infectious myocarditis, or the excessive heart demand, which was prolonged, led to a steady depletion of the cardiac reserve, ending in clinical failure and coronary insufficiency. The primary infection played an indirect etiologic role in the heart picture.

CASE 10.—M. H., a 46-year-old beauty parlor operator, accidentally short circuited a drying machine, causing the electric current to pass through her body for several minutes before she was released. She was unconscious for about fifteen minutes and then complained of rapid heart action, nausea, frequency of urination, severe headache, and a burn of the heel caused by the exit of the current. She was kept in bed for several weeks and, on getting up, noticed exertional dyspnea, precordial distress, weakness, and dizziness. The past history was normal.

She was seen three months later, complaining of mild dyspnea and heart pains. The heart, blood pressure, and electrocardiograms were essentially normal.

Comment.—This woman was in good clinical health until she sustained a severe electrical shock. She then developed signs of cardiac insufficiency without objective findings. She made a good functional recovery. The accident caused a loss of efficiency which was only temporary in nature. This case is in keeping with current reports. Gonzales[7] feels that this type of injury may temporarily depress the respiratory and cardiac centers in the brain.

SUMMARY AND CONCLUSIONS

This is a clinical study of ten cases of acute heart disease following such indirect industrial accidents as exposure to toxic gases (Cases 1 to 7), electric current (Case 10), systemic infections (Case 9), and injection of tetanus antitoxin (Case 8). The term indirect means that the offending force is not applied directly to the heart, but acts in a remote and indirect manner. Each of these cases must be evaluated on an individual basis although certain well-defined general principles must be followed.

The functional and structural damage is usually in direct proportion to the offending force, and the response of an organ to trauma is dictated by the underlying physical condition.

Certain gases are capable of affecting the heart both in the laboratory and at the bedside. They may act on the heart by producing a toxic myocarditis, interfere with normal oxygen absorption by destruction of the mucous membranes of the lung, form stable compounds with the hemoglobin, produce anemia, or displace the oxygen in the blood. Oxygen want results in an excessive demand on the heart which, if pro-

longed, is followed by structural and functional changes. Systemic infections and foreign proteins may also make excessive cardiac demands. Electrical shock produces a dysfunction without organic changes. In gas poisoning, blood tests should be done to determine the qualitative and quantitative character of the toxin. The toxic action of gases depends upon the concentration and length of exposure. It is doubtful if a casual, isolated contact can produce serious heart damage unless the gas is very concentrated. In most of the cases, symptoms appeared after toxic doses of gas had been inhaled or the heart had been subjected to a sustained demand (Cases 8 and 9). The functional evaluation may often be delayed because the patient is bedridden.

The most important factors in establishing causal relationship were the history and the circumstances surrounding each incident. Every effort should be made to check the patient's story in order to arrive at a fair clinical conclusion.

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A PHONOCARDIOGRAPHIC STUDY OF THE HEART SOUNDS IN ACUTE CORONARY OCCLUSION

ARTHUR M. MASTER, M.D., AND RUDOLPH FRIEDMAN, M.D.
NEW YORK, N. Y.

SINCE Herrick's[1] classical description of coronary occlusion in 1912, impairment of the heart sounds has maintained an important place in the diagnosis of this condition. Its clinical significance was reemphasized by Levine[2] but, in spite of the fact that excellent sound recording devices are available at present, the character and mechanism of the changes in the heart sounds have been studied phonocardiographically only by Parsonnet and Hyman[3] and Master, Dack, and Jaffe.[4] Until now the phonocardiograph has been used almost exclusively in the study of murmurs and the mechanism and physiology of the heart sounds, with scarcely any attempt to investigate the alterations of the heart sounds in the different types of heart disease and to correlate them with the clinical findings. We have therefore carried out such a study, beginning with acute coronary occlusion, preliminary results of which have already appeared.[5]

MATERIAL AND METHOD

This report is based upon observations in seventy-eight patients admitted to the hospital with acute coronary occlusion. Phonocardiograms were taken daily during the first two or three weeks and thereafter at least twice a week, until discharge from the hospital. At the time of these observations the heart sounds had not been recorded in normal persons of the same age group with the type of electric amplifying and filtering system we used. Since the inherent frequency characteristics of different sound recording devices have a varying modifying influence upon the recorded heart sounds, we collected our own control series of phonocardiograms in 100 normal persons over 40 years of age. In this age group the transmission of the heart sounds is modified by changes in the elasticity of the lungs and the thoracic cage, and the incidence of third heart sounds and auricular sounds is less than in younger persons.

The heart sounds were all recorded at the apex since it is generally the point of maximum audibility. The patient was told to hold his breath without strain at the end of a normal expiration; this excluded any effect of respiration on the intensity or pitch of the heart sounds. Phonocardiograms were always taken in the semirecumbent position to avoid

From the Cardiographic Laboratory and the Medical Services of the Mount Sinai Hospital, New York.
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possible changes due to differences in body position. The instrument used was an electric amplifying and filtering system,* the mechanics and structure of which have recently been thoroughly discussed by Rappaport and Sprague.[6] We employed two microphones of different filtering range. The first transmits all the frequencies present in the heart sound, including those below the threshold of audibility, i.e., below 35 to 40 cycles per second. The second transmits only the higher frequencies, those usually audible to the human ear. We were thus able not only to study the different frequency elements of the heart sounds but to record them as they are actually heard during auscultation.

The volume control provided in the phonocardiograph made it possible to maintain the same degree of amplification in the serial tracings of each patient. Changes in intensity, particularly those of the first sound, could thus be followed with more accuracy than had been possible previously. Sometimes, however, this principle of uniform amplification could not be adhered to strictly, due to marked and rapid changes in the intensity of the heart sounds from day to day. If they became too faint, it was necessary to increase the amplification to obtain a record suitable for the study of frequency changes. If the sounds increased markedly in intensity, the amplification had to be reduced lest the base line lose its smoothness and become distorted by vibrations set up by sounds impinging too strongly on the microphone.

Simultaneous electrocardiograms and often also simultaneous venous pulse tracings were recorded since phonocardiograms without reference tracings may lead to false interpretation of the timing and identification of the heart sounds. Orías and Braun Menendez[7] have demonstrated the value of venous pulse tracings particularly for identifying the sounds which occur in diastole, during which the electrocardiogram merely shows an isoelectric interval. The electrocardiogram is therefore of little aid in differentiating an auricular from a third sound and the latter from a split second sound, particularly in the presence of tachycardia. Moreover, the time relationship of the onset of these sounds to the T wave or to the P wave of the electrocardiogram depends too much on the heart rate to assure their accurate identification. Their relation to the waves of the venous pulse are much more constant; the third sound coincides with the descending limb of the "v" wave and the auricular sound coincides with, or slightly precedes, the peak of the "a" wave.

RESULTS

NORMAL CONTROLS

Before describing the phonocardiographic findings in the patients with acute coronary occlusion, we shall briefly present the observations in the group of 100 normal subjects, ninety-three of whom were over 40 years old and none under 32.

*Sanborn Stethocardiette.

1. *First Heart Sound: Amplitude.*—This is merely the graphic recording of the intensity of the sound and varies normally with such extracardiac factors as the elasticity of the thoracic cage and lungs, the amount of lung tissue interposed between the heart and the chest wall, and the amount and consistency of breast tissue. All these introduce difficulties in transmission, resulting in diminished amplitude and in changes in pitch of the heart sounds. Under favorable conditions of conduction the normal first heart sound shows the following configuration (Fig. 1): one or two vibrations of very low amplitude and frequency

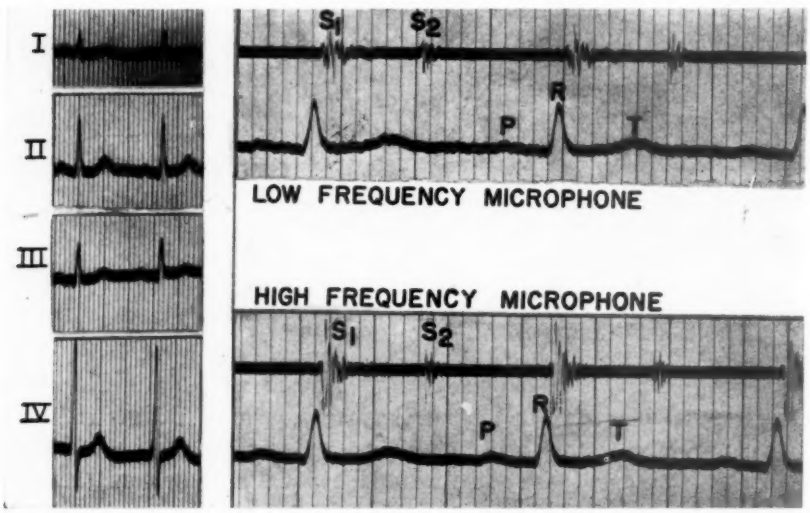

Fig. 1.—S. B. Normal male, aged 48, with normal electrocardiogram and phonocardiogram. The first sound (S_1) is of higher amplitude than the second (S_2) and shows initial low-pitched and central high-pitched vibrations. S_2 is of lower amplitude and higher frequency than S_1. In this and the following figures strips of the four-lead electrocardiogram are on the left and the phonocardiogram with simultaneous Lead II electrocardiogram on the right.

followed by a central group of vibrations of very high amplitude and frequency and finally one or two groups of vibrations of gradually decreasing amplitude. It has been established that the initial low component is auricular in origin and is caused by vibrations which continue from the auricular systole into the ventricular systole. The central group originates during the isometric contraction phase of the ventricles associated with a steep rise in intraventricular pressure. Whether it is produced by contraction of the ventricular muscle or, as many hold, by closure of the atrioventricular valves, has not been determined but is not relevant to this study. It is sufficient to emphasize the fact that these central vibrations occur during the isometric contraction phase and are therefore closely associated with the magnitude of the intraventricular pressure. The final groups of vibrations are set up during the ejection phase of the ventricular systole.

The configuration of the first heart sound just described was observed in the entire control series. Diminution in amplitude was found in six subjects (Table I). Since it affected all the components of the sound equally, it may be ascribed to extracardiac factors.

TABLE I

THE HEART SOUNDS IN SEVENTY-EIGHT CASES OF ACUTE CORONARY OCCLUSION
(Comparison With 100 Normal Subjects of the Same Age Group)

HEART SOUNDS	CORONARY OCCLUSION (%)	NORMAL SUBJECTS (%)
First Sound (S_1)		
S_1 low	24	6
S_1 lower than S_2	54	6
Auricular Sound (A_a)		
Total number	83	38
A_a of normal amplitude	50	38
A_a accentuated (presystolic gallop)	33	0
Third Sound (S_3)		
Total number	47	12
S_3 of normal amplitude	38	12
S_3 accentuated (protodiastolic gallop)	9	0
Summation Gallop (fusion of A_a and S_3)	6	0

TABLE II

ANALYSIS OF THE FREQUENCY COMPONENTS OF THE FIRST SOUND
(Comparison of Thirty Patients With Coronary Occlusion With Thirty Normal Subjects)

	LOW-FREQUENCY MICROPHONE		HIGH-FREQUENCY MICROPHONE	
	CORONARY OCCLUSION	NORMAL SUBJECTS	CORONARY OCCLUSION	NORMAL SUBJECTS
Duration (sec.)	0.09	0.10	0.08	0.07
No. of vibrations	8-9	8-9	9	8-9
Frequency				
Average	82	83	118	116
Range*	60-100	60-100	80-140	80-140

*In 90 per cent of cases; in remaining 10 per cent the frequency was slightly beyond this range.

Table II presents the number of vibrations, duration, average frequency and frequency range of the heart sounds in thirty of the 100 normal subjects with tracings recorded by both the low-frequency and high-frequency microphones. A comparison of our figures with those in the literature, as compiled by Orías and Braun Menendez,[7-12] shows close agreement in regard to the duration of the first sound but a slight, though definite, disparity in the average frequency range. This may be explained by a difference in the methods used, for our figures agree with those obtained by authors who also employed an electric amplification system[13, 14] but are higher than those obtained by the direct mechanical methods of Wiggers and Dean.[11, 12, 15, 16] We therefore accepted our own control phonocardiograms as normal. It is also evident in Table II that the vibration frequencies obtained with the high-frequency microphone were higher than those recorded with the low-frequency microphone, proof of the selective quality of the former type of microphone.

2. *Second Heart Sound.*—The second heart sound is of shorter duration and lower amplitude than the first. The first sound presented a higher amplitude in ninety-four of the normal adults over 40 years of age. In the remaining six cases the second sound was higher relative to the first sound and two of these six showed an absolute increase.

3. *Auricular Sound.*—An auricular sound (Fig. 1) was present in 38 per cent of the normal subjects (Table I), an incidence similar to that reported by others.[12, 13, 17-19] The auricular sound usually consisted of one or two vibrations of low frequency (25 to 40 cycles) and amplitude, immediately preceding the first heart sound.

4. *Third Sound.*—A third sound (Fig. 1) was noted in 12 per cent of the control cases, the expected incidence in this age group. Its incidence has been found to fall with increasing age, being present in 57 to 95 per cent of adolescents and young adults[20-22] and in only 14 to 20 per cent of older persons.[20, 23, 24] The configuration of the third sound (usually 1 vibration), its low frequency (25 to 35 cycles) and amplitude, and its relation to the second heart sound (approximately 0.10 sec. later) were similar to those generally described.[12, 14, 18, 19, 25]

5. *Gallop Rhythm.*—Gallop rhythm was never encountered in the group of control subjects, since accentuation of the auricular or third sound, which produces this abnormality, does not occur in normal adults.

MYOCARDIAL INFARCTION

1. *First Heart Sound: (a) Amplitude.*—The amplitude of the first heart sound was absolutely low in 24 per cent of the seventy-eight patients (Table I); relative to the second sound it was low in forty-two cases (54 per cent), a very much higher percentage than was found in the control group (6 per cent). This reversed relationship of the amplitude of the first and second sounds, although known to the clinician, has been studied phonocardiographically only by Parsonnet and Hyman[3] and by Master and his associates.[4, 5] As a rule, the loss of amplitude affected the central group of vibrations which normally shows the highest amplitude and frequency (Figs. 2 and 3).

The diminution in amplitude of the first heart sound usually appeared immediately after the attack; in five of the forty-two cases the alteration took place in three to ten days. The abnormality usually persisted during the period of observation of three to nine weeks but in eight patients who survived normal amplitude reappeared in one to five weeks.

(b) Frequency and Duration.—In Table II it will be seen that there was no significant difference from the values found in the control phonocardiograms in the number of vibrations, the duration or the average frequency range of the first heart sound at any time during the attack. The essential difference was the decrease in amplitude of the central group of highest frequencies (Figs. 2 and 3).

2. *Second Heart Sound.*—We have just pointed out that forty-two of the seventy-eight patients with acute coronary artery occlusion presented a diminished first sound. As a result the second sound appeared louder

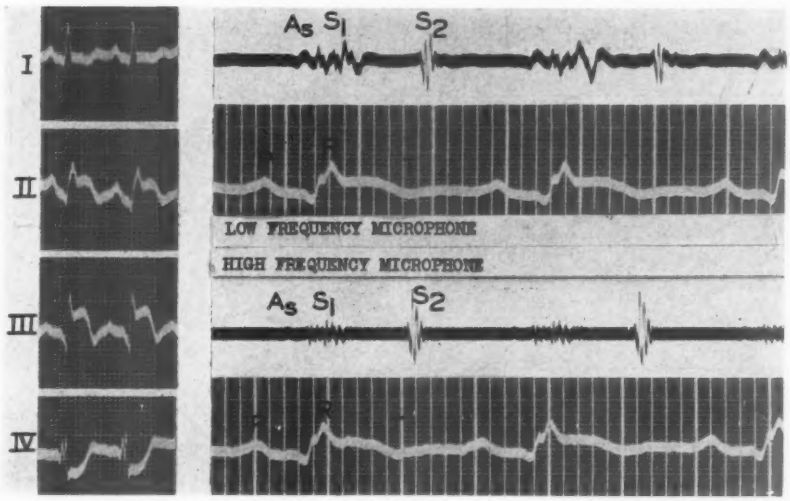

Fig. 2.—B. K. Male, aged 48. Acute coronary occlusion, fourth day. Electrocardiogram characteristic of acute posterior infarction (Q_3-T_3 pattern). Phonocardiogram reveals marked diminution in amplitude of the first sound (S_1) affecting particularly the central group of high-frequency vibrations. The second sound (S_2) is of high amplitude. A prominent low-pitched auricular sound (A_s) is present and was faintly audible.

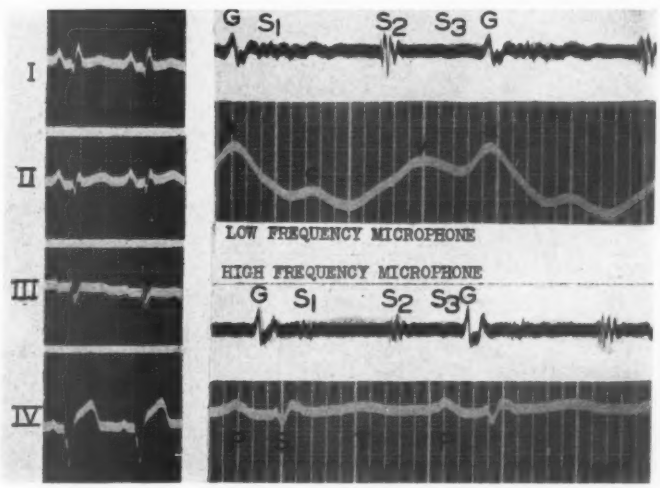

Fig. 3.—Male, aged 49. Coronary occlusion, sixth day, anterior infarction ($Q_{1\text{-}4}$-$T_{1\text{-}4}$). Phonocardiogram shows marked diminution of S_1, and presystolic gallop. The prominent gallop (G) is an accentuated auricular sound, corresponding to the "a" wave of the phlebogram. A faint low-pitched S_3 is visible.

to the ear; in addition, a good number of patients definitely gave the impression on auscultation that the second sound was actually louder than normally. In eleven cases we had definite phonocardiographic evi-

dence of this increase in amplitude of the second sound absolutely as well as relatively (Fig. 2). Parsonnet and Hyman[3] also observed this. In Table III are listed the ratios of the amplitude of the first and second sounds in serial records of these patients. These cases were chosen because the amplification of the high frequency microphone was kept constant throughout the patient's illness (usually 6½ to 8).

TABLE III

CONCOMITANT CHANGES IN AMPLITUDE OF FIRST AND SECOND SOUNDS IN CORONARY OCCLUSION

CASES	S_1 TO S_2 (MM.)	S_1 TO S_2 (MM.)
1	5 : 8	10 : 3¼
2	11 : 4½	3½ : 16
3	6½ : 9	5¼ : 13½
4	9 : 4	4 : 10
5	3 : 5	4 : 10½
6	5 : 3	3 : 10
7	6 : 9½	4½ : 12
8	11½ : 9	8 : 16
9	4½ : 13	11½ : 7
10	9 : 4	6 : 15
11	7 : 6	3½ : 12

3. *Additional Heart Sounds: (a) Auricular Sound.*—An auricular sound was present in 83 per cent of the patients. In 50 per cent it was not significant since it showed the same configuration (1 to 2 vibrations of low frequency and amplitude) observed in 38 per cent of the normal phonocardiograms. The remaining 33 per cent of the auricular sounds in the coronary group were significant since they showed increased amplitude and formed a presystolic gallop. The latter is discussed later.

(b) Third Sound.—This sound was present in 47 per cent of the patients. It showed the normal configuration of the third heart sound found in 12 per cent of our control group, except for 9 per cent in which the amplitude was increased, giving rise to a protodiastolic gallop.

(c) Gallop Rhythm.—Working independently Wolferth and Margolies,[26] Battro, Braun Menendez and Orías,[27] and also Duchosal[28] arrived at the conclusion that the sounds forming gallop rhythm represented merely an exaggeration of phenomena normally present but often inaudible because of their low amplitude and frequency. Taking simultaneous phonocardiograms and phlebograms for the proper identification of the gallop sound and using the classification proposed by Wolferth and Margolies,[26] these authors showed that a presystolic gallop was produced by an auricular sound of increased amplitude and that a protodiastolic gallop represented an accentuated third sound. A summation gallop was formed by the superimposition of the auricular and third sounds of normal or accentuated amplitude, this fusion being complete or incomplete depending upon the heart rate. In our series a presystolic gallop occurred in 33 per cent of the patients (Table I) and was associated with heart failure in twenty-four of the twenty-six cases

(Table IV). It is of interest that each of the twenty-four cases had a first heart sound of diminished amplitude (Fig. 3). A protodiastolic gallop (Fig. 4) was found in only 9 per cent of the patients, and a summation gallop, in only 6 per cent, all of these also being associated with manifest heart failure.

TABLE IV

CORRELATION BETWEEN HEART FAILURE AND HEART SOUNDS IN CORONARY OCCLUSION

	NO. OF CASES	HEART FAILURE	
		PRESENT	ABSENT
$S_1 < S_2$	42	37 (88%)	5 (12%)
$S_1 =$ or $> S_2$	36	12 (33%)	24 (67%)
Gallop rhythm	38	36 (95%)	2 (5%)

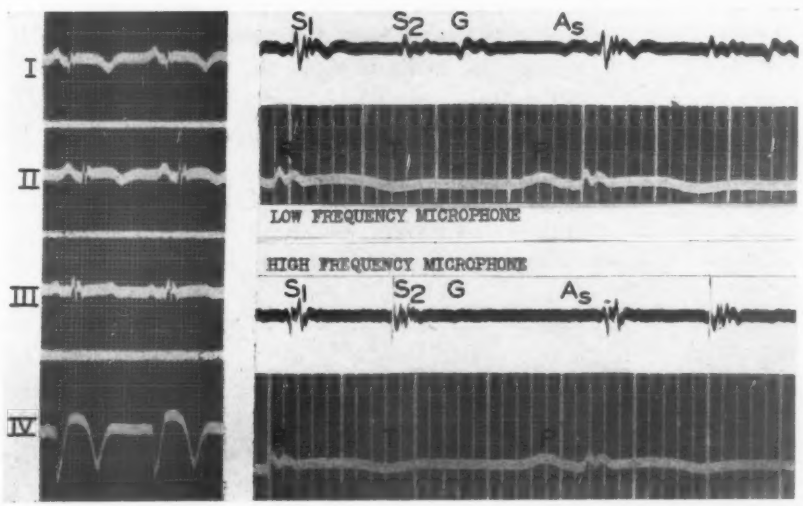

Fig. 4.—M. H. Male, aged 42. Acute coronary occlusion, fourth week. Electrocardiogram characteristic of recent anterior infarction (Q_{1-4}-T_{1-4} pattern). Phonocardiogram shows diminished amplitude and loss of high-pitched components of the first sound (S_1) and protodiastolic gallop rhythm (G) due to an accentuated third heart sound. A normal auricular sound (A_s) is also visible preceding S_1. All these findings were present since the second day of the attack.

COMMENT

First Sound.—We have shown that changes in the character of the first heart sound usually occur immediately following an attack of acute coronary artery occlusion and persist throughout the illness. The use of low-frequency and high-frequency microphones revealed diminution in amplitude of the central group of vibrations which normally are of very high amplitude and frequency and which occur during the isometric contraction phase of the ventricles.

This change in the first sound is audible as a "dull, muffled" or "poor" sound. Since the number of vibrations, the duration, and average frequency of the first sound did not show any significant change

from normal, the explanation of the peculiar change in pitch of the first sound must be sought in the diminution in amplitude of the central group and in the so-called masking effect.[29] The latter implies that a low-pitched sound of great intensity "masks" a sound of higher pitch which is not too distant from it in the frequency scale but of comparatively lesser intensity. Thus, the masking of the faint high-frequency components of the first sound by the relatively prominent low-frequency elements produces the auscultatory impression of a dull, muffled or poor first heart sound in coronary occlusion. However, in the phonocardiogram recorded with a proper filtering and amplifying system, all the frequencies, while diminished in amplitude, are present in a number not differing from the normal.

It seemed logical to consider the loss of amplitude of the first sound the result of lowered intraventricular pressure resulting from the impaired contractility of the infarcted ventricular muscle. Perhaps this is a factor in the first few days or more, when the patient is acutely ill, the cardiac output diminished, and the blood pressure low. However, this explanation does not account for the persistence of the low first sound after the patient has recovered from the initial phase of the attack, and often for months and years later when the patient's condition may be good, without heart failure, and with normal blood pressure and cardiac output. Hence one must assume that some change in the physical properties of the damaged left ventricle is the cause of the diminution in amplitude of the central group of vibrations of the first heart sound.

The great majority of patients (37 of 42) with this type of diminished first sound showed signs of heart failure while those with an unimpaired first heart sound developed none or only a very mild and transient degree (Table IV).

The change in the character of the first sound in coronary occlusion is of diagnostic importance. We have seen that it is present in 79 per cent of patients during the acute and subacute phases and a follow-up study of patients who have recovered from coronary occlusion reveals a tendency for it to persist for years. Only a limited number of follow-up patients have been studied phonocardiographically, but in a clinical investigation[30] of 202 cases followed for an average period of three years after the acute attack it was found that the first sound remained of abnormally low pitch and intensity in half the cases. An impaired first sound may be the only sign remaining after an acute attack of coronary occlusion, and, whenever it is found in a person of the coronary age group, the possibility of a previous attack of acute coronary occlusion should be borne in mind.

Second Heart Sound.—The explanation of the absolute increase in the second heart sound which occurs not infrequently in coronary occlusion is not clear. It is accepted that the second heart sound is produced by

closure of the semilunar valves and is transmitted through the ventricular muscle toward the apical area of the chest. When the ventricle is infarcted, the change in its physical quality may make for increased loudness of the second sound while at the same time it diminishes the amplitude of the first sound.

Additional Heart Sounds: (a) Auricular Sound.—A low-pitched sound of low amplitude preceding the first sound is a frequent normal finding, physiologically related to auricular systole. In coronary occlusion, however, the incidence of auricular sounds is much higher (83 per cent); and auricular sounds of abnormally high amplitude are common (33 per cent), forming presystolic gallop rhythm associated with heart failure.

(b) Third Sound.—It is generally accepted[7, 8, 19, 22, 24, 25, 31, 32] that the normal third sound of low pitch and amplitude is closely related to the phase of rapid ventricular filling in early diastole. Immediately after the opening of the atrioventricular valves at the onset of diastole the blood rushing into the ventricles impinges on their elastically-responding walls, thus setting up vibrations which form the third sound. Whatever impairs the tonus of the ventricular muscle, thus increasing its distensibility, or causes it to overact tends to produce a third sound of higher intensity. A third sound due to an overacting heart occurs in adolescence, thyrotoxicosis, anemia, and neurasthenia.[7, 20, 22, 25, 36] In adults third sounds are uncommon and, when present, are usually of lesser intensity. This has been ascribed to the greater tonus of the adult heart muscle, but the poorer conduction through the more rigid and thicker chest wall is of equal importance. Following coronary occlusion the infarcted ventricular muscle loses its normal tonus and the ventricle dilates; therefore, third sounds are more frequent and of greater intensity. This is well borne out by our data.

(c) Gallop Rhythm.—Gallop rhythm was noted by clinicians as early as 100 years ago,[33] but its mechanism and significance were not clearly understood until the introduction of optical methods of recording heart sounds and simultaneous venous pulse tracings.[28, 34-37] The term gallop rhythm was then restricted to the accentuation of auricular and third heart sounds and their superimposition. In addition, it was recognized that gallop rhythm was associated with heart failure, and the French authors[28, 36, 37] and Wolferth and Margolies[26] used the term only when heart failure was present. Our own experience in a great number of patients has demonstrated that gallop sounds may be present before frank signs of heart failure appear. It is in these cases particularly that phonocardiograms gain clinical importance since they often record gallop sounds missed by auscultation because of their low pitch or unfavorable conduction to the chest surface. With proper filtering and amplification these clinical inaudible sounds are recorded and often heart failure becomes clinically manifest soon thereafter. The frequency of

heart failure in coronary occlusion[4] accounts for the high incidence of gallop rhythm (47 per cent).

The close association of gallop rhythm with heart failure was apparent in our series in which all but two of thirty-eight patients presenting gallop rhythm had heart failure (Table IV). Any of the three types of gallop rhythm may be associated with heart failure, but the presystolic type is most frequently found. The cause probably is the increased intra-auricular pressure present in heart failure. The high incidence of gallop sounds in coronary occlusion cannot be regarded as specific since true gallop rhythm is also found in heart failure due to hypertensive or rheumatic heart disease. However, the association of gallop rhythm and impaired first heart sound in coronary occlusion deserves particular emphasis since it is rarely encountered in heart failure due to other causes.

SUMMARY

A phonocardiographic analysis employing microphones of different frequency filtering and transmission range was made of the heart sounds in seventy-eight cases of acute coronary occlusion and in 100 normal control subjects. The results were correlated with the clinical findings.

The first heart sound was absolutely diminished in amplitude in 24 per cent and relatively to the second sound in 54 per cent of the patients with acute coronary occlusion. This diminution in amplitude affected the central group of high-frequency vibrations and was attributed to the change in the physical character of the infarcted left ventricle and possibly, in the first few days of illness, to the lowered intraventricular pressure following acute myocardial infarction.

Occasionally the second sound at the apex is increased to an absolute as well as a relative value.

An auricular sound was present in 83 per cent of cases of coronary occlusion compared to 38 per cent in normal subjects. In one-third of the cases of coronary occlusion the auricular sound was accentuated and formed presystolic gallop rhythm. This never occurred in normal subjects. Accentuation of the auricular sound was probably the result of the increased intra-auricular pressure following ventricular infarction. It was practically always associated with heart failure.

A third sound occurred in 47 per cent of the cases of coronary occlusion as compared to 12 per cent in normal subjects. The high incidence in the former was attributed to the decreased tonus of the infarcted ventricular muscle. In 9 per cent of the cases the third sound appeared accentuated and produced protodiastolic gallop rhythm. Heart failure was invariably associated with it.

Superimposition of the auricular and third sounds of normal or accentuated amplitude occurred in 6 per cent of cases, forming summation gallop. This type of gallop rhythm was also associated with heart failure.

Clinical heart failure was present in 63 per cent of the cases of coronary occlusion. It occurred predominantly in those who presented a first sound of diminished amplitude (88 per cent) and gallop rhythm (95 per cent). It was much less common in those with an unimpaired first sound (33 per cent). This emphasizes not only the close relationship between impaired heart sounds and heart failure but also the serious import of a diminished first heart sound and gallop rhythm.

Gallop rhythm may be present before signs of heart failure are apparent.

The impairment of the first heart sound following coronary occlusion is often permanent and may be the only persistent sign following recovery. It thus may be of diagnostic significance.

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SPONTANEOUS CHANGES IN THE NORMAL RABBIT ELECTROCARDIOGRAM

HAROLD D. LEVINE, M.D.
BRISTOL, N. H.

AS A COROLLARY to another research, it was necessary to make a control study of the spontaneous day-to-day variations in the normal rabbit electrocardiogram. Although similar controls may have been made in the course of other electrocardiographic investigations on rabbits, they must be considered as buried, as it were, and hence unavailable as a standard for future reference. A careful search of the literature, moreover, revealed no publication dealing purely with the normal rabbit electrocardiogram. In order, therefore, to avoid further unnecessary and uneconomical duplication of effort, and because the present research did show considerable spontaneous variation in the appearance of the tracings, awareness of which might keep the investigator in this field from going astray, presentation of these observations is considered desirable.

METHOD

In these experiments, five-lead electrocardiograms were taken on every second, third, or fourth day with a vacuum-tube type of electrocardiograph (Cardiette). The skin was first clipped or shaved over an area about the size of an ordinary surface electrode on the left and right forelegs and the left hind leg close to the trunk, and over the anterior surface of the chest. In a few instances barium sulfide was used as a depilatory, and this saved a good deal of time. The bare areas were then rubbed with Redux electrode paste, and the surface electrodes were applied and kept in position with elastic bands. In addition, chest leads were taken by applying an electrode to the chest wall and attaching it to the left leg cable; this was coupled with the left arm cable, attached to the left leg electrode. The tracings were then taken with the lead switch on Lead III. Two chest leads were taken, one from the left and the other from the right side of the anterior surface of the thorax. In both cases the cephalic end of the electrode impinged exactly in the apex of the axilla and the median side of the electrode was exactly in the midline of the sternum. The animal was allowed to assume a natural prone position, and, after initial evidences of fear had subsided, and it was made certain that there was no rotation of the thorax about its longitudinal or transverse axis, the tracings were taken. The use of restraint was avoided as far as possible. In a few cases, fright could be overcome by putting a loose towel over the animal's head. The records were carefully standardized so that 1 millivolt produced a deflection of 1 cm.

Because of the looseness of the skin over the rabbit's chest, it was difficult to be sure that exactly the same relationship held between the position of the electrode and the position of the heart at different times. Nor would this difficulty be obviated by the use of needle electrodes. However, in several instances the chest leads were re-

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peated after removing and reapplying the chest electrodes, and identical tracings were obtained. By removing and deliberately reapplying the chest electrode 1.5 cm. mesiad, laterad, cephalad, or caudad to its original application, marked differences in the appearance of the tracing were produced. Such changes could easily be produced by inadvertently sliding the skin over the thorax in applying the chest electrodes. The appearance of the conventional limb leads, by contrast, is very little if at all affected by slight differences in the application of the electrode to the limb. Accordingly, it is felt that greater importance must be attached to spontaneous changes in the conventional leads than in the chest leads.

On nine normal male rabbits, ranging in weight from 1.5 to 3.0 kg., five-lead electrocardiograms were taken at intervals of one to four days for a period of two weeks; on the average, one series of tracings was taken every other day. Also included in this study are the initial control tracings from a series of fourteen animals that subsequently formed part of another investigation.[1] Thus multiple observations are available on nine, and single observations on fourteen, rabbits, making a total of twenty-three animals. A total of 335 records was obtained on these twenty-three rabbits. As far as possible, the tracings were made at about the same time of day and at about the same time after eating. A comparator was used to measure the height of the various components of the tracings. When the height of an individual wave varied from complex to complex, as it frequently did, the average of several measurements was recorded. Daily recordings were made of the rectal temperature. The nine animals on which repeated electrocardiograms were made were sacrificed after the final electrocardiograms, and numerous microscopic sections were made of the heart. In no case were pathologic changes found.

RESULTS

Static Considerations.—The results are best expressed in the form of a composite tabulation giving the minimum and maximum, as well as the median and mode, of all the measurements made on the twenty-three animals (Table I). It should be noted that just as many observations exceed as are exceeded by the *median* value in height or duration. The *mode*, on the other hand, is the measurement most frequently made. In this discussion Lead L refers to the derivation from the left anterior chest, and Lead R, to that obtained from the right anterior chest.

The P wave, when measurable, was usually upright, but occasionally inverted, in Leads I and L. It was occasionally inverted, but usually upright, in Lead III. It was always upright in Lead II. In Lead R, the P wave was usually inverted, occasionally diphasic, but never purely upright.

The P-R interval varied from 0.06 to 0.09 in Lead I, from 0.06 to 0.10 in Leads II and III, and from 0.06 to 0.08 in the chest leads (L and R), but the median and mode for all leads was 0.07 second. A Q wave was more often present than absent in Leads I and L. It was generally absent in the other leads, but depths of 1.6 to 6.5 mm. were recorded occasionally. Very frequently there was no R wave in Lead I; this wave was generally well developed in all the other leads, especially Lead II. The S wave, too, was, more often than not, absent in Lead I. It was occasionally present in Lead II, and usually well marked in Leads III and R. It was present in about half the tracings in Lead L.

The duration of the QRS complex was almost invariable; it measured 0.03 second in the great majority of records. In only a very exceptional case did it approach 0.04 second.

TABLE I

COMPOSITE TABULATION OF ELECTROCARDIOGRAPHIC MEASUREMENTS ON TWENTY-THREE NORMAL, UNANESTHETIZED, MALE RABBITS

		LEAD				
		I	II	III	L	R
P (mm.)	Min.	-0.2	+0.4	-0.4	-1.0	-1.2
	Max.	+1.3	+2.0	+1.7	+1.0	-0.2*
	Mode	+0.3	+1.0	+0.5	+0.5	-
	Median	+0.3	+1.0	+0.8	+0.5	-0.6
P-R (sec.)	Min.	0.06	0.06	0.06	0.06	0.06
	Max.	0.09	0.10	0.10	0.08	0.08
	Mode	0.07	0.07	0.07	0.07	0.07
	Median	0.07	0.07	0.07	0.07	0.07
Q (mm.)	Min.	-2.5	-1.6	-4.5	-2.7	-6.5
	Max.	0	0	0	0	0
	Mode	0	0	0	0	0
	Median	-0.1	0	0	-0.4	0
R (mm.)	Min.	0	+2.6	0	0	0
	Max.	+8.0	+7.5	+7.0	+7.0	+3.7
	Mode	0	+3.6	-	+1.4	+1.6
	Median	+1.3	+3.5	+3.3	+1.4	+1.6
S (mm.)	Min.	-1.5	-4.0	-3.7	-5.0	-9.0
	Max.	0	0	0	0	0
	Mode	0	-	-0.5	0	-2.2
	Median	0	-0.9	-1.1	-0.2	-2.2
QRS (sec.)	Min.	0.03	0.03	0.02	0.03	0.03
	Max.	0.04	0.04	0.04	0.03	0.04
	Mode	0.03	0.03	0.03	0.03	0.03
	Median	0.03	0.03	0.03	0.03	0.03
T (mm.)	Min.	-1.2	+0.5	-4.0	-0.2	-4.0
	Max.	+4.4	+4.0	+2.5	+2.2	+1.5
	Mode	+1.1	+1.5	-	+1.0	-1.6
	Median	+1.1	+1.5	+0.8	+1.0	-1.5

*Twice diphasic.

In only one lead, Lead II, was the T wave constantly upright. No instances of inversion of T_2 occurred in this series. In only one case was T_1 inverted. In all the others it was upright. T_3 was usually upright, but frequently inverted. T in Lead L was occasionally inverted. T in Lead R was usually inverted; in only two instances was T upright in Lead R in this series. In several instances there was no isoelectric interval between the QRS complex and the T wave; the latter tended rather to run or slope down or up immediately on the completion of the R or S wave.

The heart rate of the rabbit, unrestrained and unanesthetized, varies between 174 and 282, with a median value of 225 beats to the minute.

Dynamic Considerations.—Although the animals were in identical positions when the electrocardiograms were taken on different days, changes in the voltage of the P waves, of the QRS complexes, and of the T waves were the rule rather than the exception. In many cases there

was reversal in the direction of the major deflection of the QRS complex. In Fig. 1, for example, the major QRS_1 deflection is downward in the first (Sept. 22, 1941) and last (Oct. 4, 1941) tracings, but upright in the intervening ones. Similarly, in Fig. 2, although the exploring electrode was applied identically at all times, the major QRS deflection in the left chest lead was upright in the first (Sept. 22, 1941), fourth (Sept. 27, 1941), and fifth (Oct. 1, 1941) tracings, but downward in the second (Sept. 24, 1941) and third (Sept. 26, 1941). Changes in the voltage and form of the T wave were much more striking and frequent. In Fig. 1, T_1 is sharp and measures 2.4 mm. in height (Sept. 22, 1941).

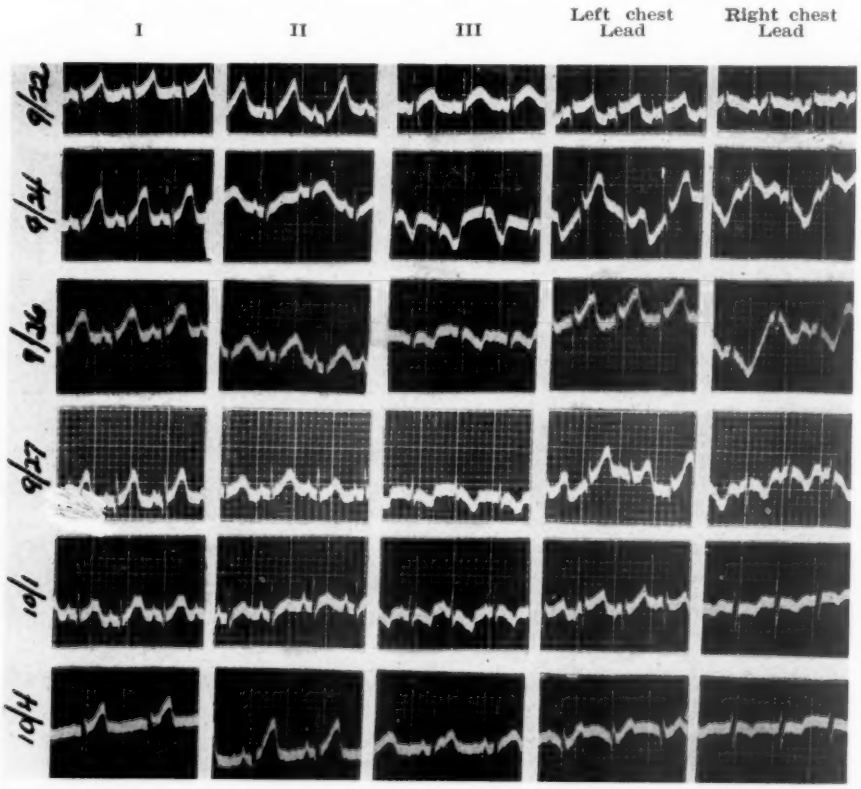

Fig. 1.—Serial, five-lead electrocardiograms from rabbit, showing (1) spontaneous variations in the voltage of the QRS complex, (2) spontaneous inversion of T_3, with subsequent return to upright position, (3) change in the contour of T_1 from sharp to rounded, with subsequent return to sharp outline, and (4) persistent, slight elevation of RS-T in Lead L.

On the next occasion it was more rounded and measured 4.1 mm. in height. Spontaneous reversal in the direction of the T wave in all leads, except Lead II, is another feature of the normal rabbit electrocardiogram. This was recorded only once in Lead I, but, in over half the cases in which repeated electrocardiograms were taken, there was spontaneous T_3 inversion, with subsequent return to the upright direction.

T_1, although generally upright, likewise frequently showed variation in voltage and occasionally reversal of direction. T in Lead R was generally inverted, but in two cases it was upright for a time. These variations are well illustrated in Figs. 1 and 2. In the former, slight deviations of the RS-T segment are also shown. Such deviations never exceeded 1 mm.

Although the P-R interval showed spontaneous variations of 0.01 to 0.02 second, its total duration never exceeded 0.10 second in the conventional limb leads or 0.08 second in the chest leads. In several instances there was spontaneous lengthening of the P-R interval from 0.07 to 0.08 or 0.09 second, without change in the heart rate. In the few cases in which the P-R interval was 0.10 second, there was an associated slowing of the heart. The duration of the QRS complex was invariable (0.03 second).

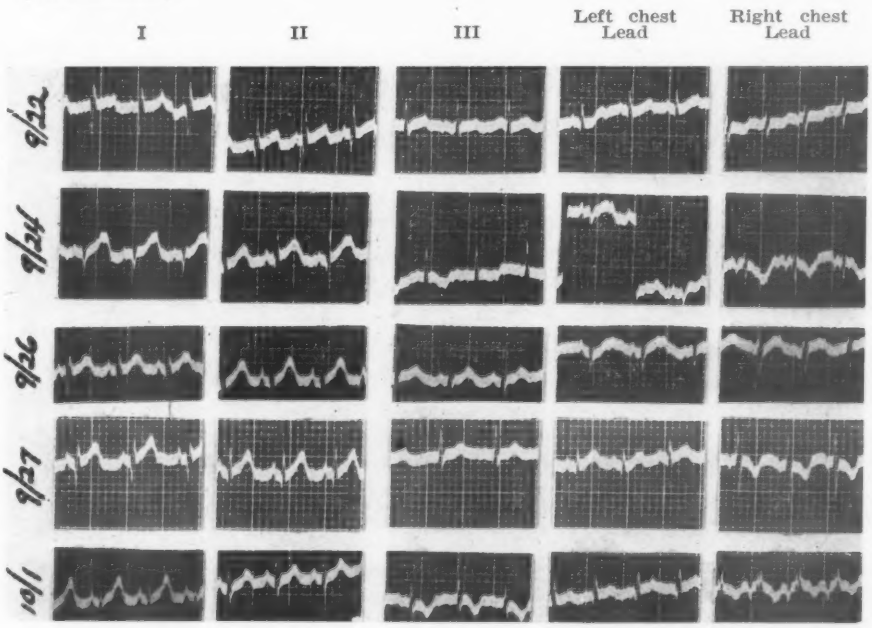

Fig. 2.—Serial, five-lead electrocardiogram from rabbit, showing (1) spontaneous variations in the voltage of the P wave, QRS complex, and T wave, (2) spontaneous inversion of T_3 at second and fifth recordings, (3) spontaneous reversal of T in Lead R from inverted to upright direction at third recording, with subsequent return to inversion, and (4) transient, slight elevation of RS-T_2.

There were no instances of transient or permanent extrasystoles, auricular fibrillation or flutter, auricular or ventricular tachycardia, intraventricular block, bundle branch block, or auriculoventricular heart block in this series of observations. Tracings from a struggling, restrained animal, preceding and during the infusion of a solution into the ear vein, did show frequent ventricular extrasystoles, with bigeminal and trigeminal rhythm, but, as stated above, such changes were not observed in the unrestrained animal.

COMMENT

Vizer and Haban[2] noted the variability of the rabbit electrocardiogram from animal to animal, but they did not describe serial changes in individual animals. The present observations are in accord with those of Becke, Johnson, and Harris,[3] who, likewise, found no major disturbances in the conduction mechanism, but these investigators failed to find T-wave changes in their control animals, and attached considerable importance to changes in the T waves which became diphasic or inverted. It emerges from the present study, however, that similar importance can be attributed to such changes only if they are present in Lead II, for they may occur spontaneously in any of the other leads.

Such changes as have been recorded may be due to variations in the vagus mechanism,[4] to extreme mobility of the rabbit's heart, producing unavoidable changes in the position and hence of the electrical axis of the heart (such as Katz, Soskin, and Frisch[5] have assumed is the case in the dog's heart), or to intrinsic electrochemical changes in the heart itself. It is the purpose of this report merely to record the fact that there are such changes, not to establish their mechanism.

SUMMARY

The rabbit electrocardiogram exhibits marked spontaneous changes in the form, voltage, and direction of many of its components. Transient reversal of the T wave in Leads I and II and in the chest leads is frequently observed. T_2 is constantly upright. Slight RS-T segment deviations, never exceeding 1 mm., are frequently encountered. The P-R interval never exceeds 0.10, and the duration of the QRS complex never exceeds 0.04, second. Abnormal rhythms are not seen in the normal, unrestrained, unanesthetized rabbit.

Cognizance of these spontaneous changes in the rabbit electrocardiogram is essential to the intelligent appraisal of experimental studies on the rabbit heart.

My sincerest thanks are due John H. Westfall, V.S., for his assistance in carrying out these experiments.

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AURICULAR FIBRILLATION OF LONG DURATION IN RHEUMATIC HEART DISEASE

CHARLES E. KOSSMANN, M.D., AND CHARLES A. R. CONNOR, M.D.
NEW YORK, N. Y.

AURICULAR fibrillation is generally regarded as a terminal event in the course of rheumatic heart disease. The permanent establishment of this arrhythmia after the age of 30 years in a person with rheumatic heart disease is a grave prognostic omen, as the mean duration of life is two years[1, 2]; the prognosis is even more grave when auricular fibrillation begins before the age of 20, as the mean duration of life is then less than one year.[1-3] The life expectancy curve of adults with rheumatic heart disease and auricular fibrillation is positively skewed[1]; that is, it shows that only 25 per cent will live three years or longer after the onset of the arrhythmia. A few live as long as ten years.

In a group of 276 adults with rheumatic heart disease and auricular fibrillation studied by DeGraff and Lingg,[1] the longest period a patient lived was twelve years. Levine[4] observed a case of this kind for seventeen years. Bishop and Bishop[5] have reported a patient with auricular fibrillation of twenty-five years' duration. The onset occurred at the age of 55 years. Necropsy revealed atherostenosis of the left coronary artery, in addition to rheumatic mitral stenosis. It is likely that arteriosclerosis was the etiologic factor in this instance rather than rheumatic infection because of the onset of the arrhythmia at a rather advanced age.

The three cases herein reported were unusual in that each had mitral stenosis of rheumatic origin with auricular fibrillation of fourteen, sixteen, and twenty-one years' duration, respectively. The abnormal rhythm began in each subject at an early age, and death occurred at 57 years, 33 years, and 45 years (Table I). This fact combined with other clinical data, and the pathologic findings observed in one of these patients make it likely that rheumatic fever was the only etiology involved in all three instances.

CASE 1.—S. A., a white male, was told he had heart disease when he was 15 years old. At 23 he had "rheumatism" of both ankles for one month. About the same time he noted a soft penile sore. No further details of this lesion are available. On July 10, 1914, during his twenty-fourth year, he was admitted to Bellevue Hospital in congestive heart failure. In the next four years he was admitted six

From the Department of Medicine, New York University College of Medicine, and the Cardiac Clinic of the Third (New York University) Medical Division, Bellevue Hospital.

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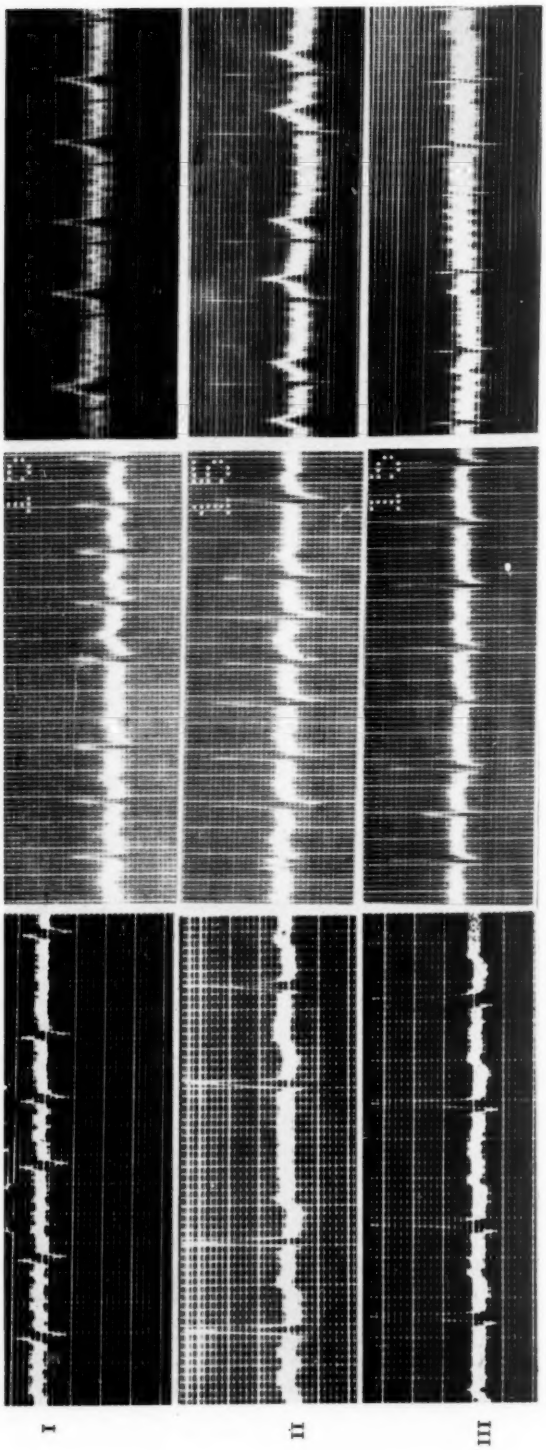


A. *B.* *C.*

Fig. 1.—*A*, S. A., Nov. 19, 1915. *B*, J. A., March 24, 1922. *C*, S. Y., April 13, 1925.

additional times, with the same syndrome, for an average stay of five weeks each time. With bed rest and digitalis he would improve, only to lapse into failure shortly after resumption of moderate physical activity. Of interest was the occurrence of hoarseness during the first nine months of observation.

On each admission between 1914 and 1918 the heart was enlarged. Presystolic and systolic thrills were felt, and corresponding murmurs were heard, at the apex. On occasions a systolic murmur, a diastolic murmur, or both, were heard in the aortic area; at other times neither one was audible. Two observers noted a systolic murmur in the tricuspid area, and one of these heard a diastolic murmur as well in 1915. The pulmonic second sound was always louder than the aortic second. The pulse was rapid, irregular in rate and force, and small. The ventricular rate, without the benefit of digitalis, varied from 100 to 180 beats per minute with a pulse deficit of 25 and 60 beats. The blood pressure range was from 110/70 to 170/100.

Other physical findings were those of congestion; i. e., distended veins of the neck, râles at the bases of the lungs, large tender liver, and edema of the ankles. Fluid was noted in the right side of the chest and was removed in amounts from 480 c.c. to 1,200 c.c. on four different occasions between 1914 and 1916. A fluid wave in the abdomen was always equivocal.

Evidence of rheumatic activity, other than heart failure and auricular fibrillation, was usually scanty.[6] The first few days of each admission the temperature was approximately 101° F., but soon fell below 99.6° F., and with a few brief exceptions remained there until his discharge. Leucocyte counts on admission were also slightly elevated. The blood Wassermann reaction was positive (12 to 15 units) in 1914, but thereafter was negative. Iodides orally and twenty intramuscular injections of mercury salicylate were the only antisyphilitic therapy given.

The first electrocardiogram was recorded on Nov 9, 1915. It displayed auricular fibrillation with a low T_1 and a diphasic T_2 and T_3, and right axis deviation (Fig. 1*A*). Subsequent electrocardiograms showed no significant changes.

From April, 1918, to April, 1923, the patient attended the clinic irregularly but took digitalis most of the time. He was regarded as having rheumatic heart disease with mitral stenosis and insufficiency complicated by auricular fibrillation. Functional tricuspid insufficiency was thought to have existed during his bouts of failure.

From 1923 to 1934 his case was not followed. In February of the latter year he was readmitted to the hospital because of increasing weakness, dyspnea and orthopnea of one month's duration, all of these symptoms having followed an upper respiratory infection. In the interim of eleven years he had been working steadily as a shipping clerk and had taken digitalis during the winter months only. On several occasions he had slight ankle edema, but only once (in March, 1933) was it severe enough to cause complete bed rest.

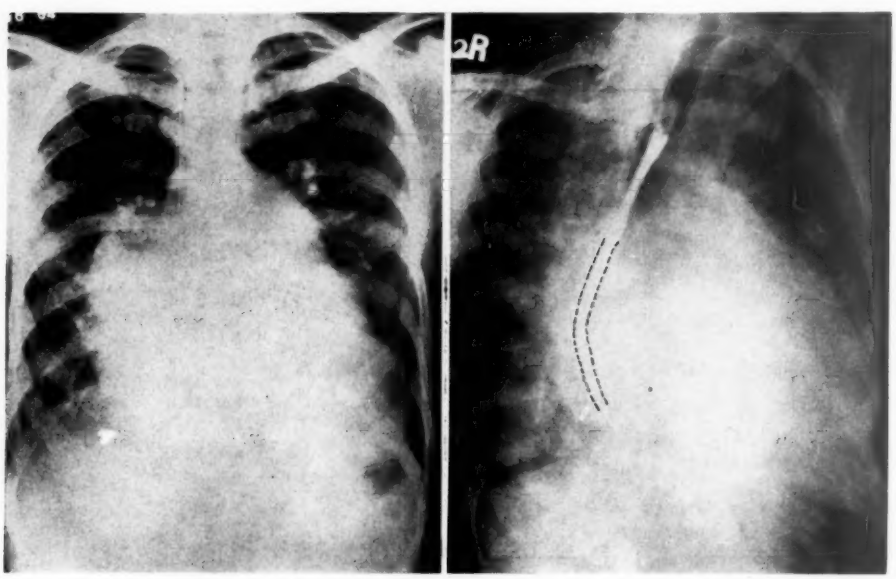
The only new physical finding was a paralyzed left vocal cord.[7] Hoarseness had been present for a year. The ventricular rate was 80 beats per minute although digitalis had not been taken regularly. The only evidence of rheumatic activity was a slight increase in the leucocyte count and a rapid sedimentation of the erythrocytes. A teleroentgenogram of the chest (Fig. 2*A*) revealed an unusual cardiac silhouette, characterized by prominent bulges on both sides, somewhat higher on the right, which was interpreted as a greatly enlarged left auricle. An esophagogram (Fig. 2*B*) showed considerable posterior displacement of the esophagus by the left auricle.

The patient quickly improved on rest in bed and digitalis. From March, 1934, to Oct. 24, 1935, he was ambulatory on whole leaf digitalis, 0.2 Gm. daily. On his last visit to the clinic on the latter date he complained of increasing dyspnea, vague pains in the abdomen, and anorexia. Vomiting began on November 9.

The patient entered the hospital for the ninth and last time on November 14. He was acutely ill. Abdominal distention and rigidity were marked. Blood was discovered in the vomitus and in the stool. The temperature was 101° F., and there was no leucocytosis. Heart failure was not marked. His course was rapidly downhill, and he died Nov. 18, 1935, at the age of 45 years, of what was thought to be a mesenteric thrombosis with infarction of the intestine.

Necropsy.—Only the important pathologic changes are noted.

Heart (Gross Examination).—The weight was 700 Gm. There was extreme dilatation of the left auricle with atrophy of myocardium and marked endocardial sclerosis. Epicardial fibrosis of the left auricle was present. Organizing thrombi were found in both auricular appendages. Marked hypertrophy and replacement fibrosis of the right auricular myocardium and old infarction of the right crista terminales were evident.



A. *B.*

Fig. 2.—*A*, S. A., April 16, 1934. *B*, S. A., Feb. 27, 1934.

Heart (Histological Examination).—There were healed mitral valvulitis (rheumatic type) with calcification and stenosis, healed tricuspid valvulitis or persistent vascularization of the leaflet, persistent vascularization of the pulmonic valve, aortic valvular sclerosis or healed valvulitis, and diffuse perivascular and moderate interstitial replacement fibrosis of the ventricles.

Aorta.—Atherosclerosis was evident in the aorta.

Lungs.—Obliterative pleuritis was seen in the right lung. Both lungs showed emphysema, congestion, pulmonary atherosclerosis, and moderate anthracosis.

Liver.—Cardiac cirrhosis with fatty change was noted.

Spleen.—Chronic passive congestion and arteriolar sclerosis were present in the spleen.

Gastrointestinal Tract.—There were hemorrhagic infarction of the ileum (gangrene), submucosal hemorrhages of the stomach, congestion of the small intestine, and acute serofibrinous peritonitis.

Kidneys.—Arteriolar nephrosclerosis, multiple healed infarcts, and congestion were observed.

It is to be noted that no evidence of rheumatic activity was found and that no occlusive disease was discovered in the abdominal cavity to account for the gangrenous ileum. A potential source of emboli, however, was found in both auricular appendages.

CASE 2.—J. A., a white female, had frequent sore throats since the age of 3, and pains in the muscles and joints, especially in the winter and spring, since the age of 7. She never had a typical attack of polyarthritis or chorea.

At 9 years she experienced dyspnea on effort accompanied by orthopnea, cough, and palpitation. The diminution of her cardiac reserve progressed in the next two years to cardiac failure, for which she entered another hospital at the age of 11 years. An enlarged heart and evidence of mitral stenosis and insufficiency were discovered at this time, but no notation was made of an arrhythmia. After two months of complete rest in bed, she was discharged improved.

Between the ages of 11 and 16 years she was free from symptoms of heart failure but continued to have frequent sore throats and pains in the muscles. The second episode of heart failure occurred in December, 1921, at the age of 16, at which time she was first admitted to Bellevue Hospital. Auricular fibrillation was noted then and at all subsequent examinations. The heart was enlarged, and there was clinical evidence of stenosis and insufficiency of the mitral valve. Digitalis was begun at this time, and she was discharged in March, 1922, improved.

The first electrocardiogram was recorded in the cardiac clinic on March 24, 1922. It showed auricular fibrillation with a ventricular rate of 140 per minute. There were no other abnormalities (Fig. 1*B*). Repeated electrocardiograms in subsequent years were similar.

She attended the clinic regularly for the next eleven years with little change in her cardiac status. In this period she took 0.2 Gm. whole leaf digitalis daily. There were no definite signs of rheumatic activity other than the fact that she developed aortic insufficiency in 1928. Her functional capacity remained good.

She had completed college and was working in 1932 when she began to develop fatigue, dyspnea, orthopnea, and cough. As these symptoms increased, despite extra rest at home, she was readmitted to the hospital on March 29, 1933, in severe congestive heart failure. There were basal pulmonary râles on admission, and later she developed a moderate effusion in the right pleural cavity. The liver was greatly enlarged. There was massive edema of the lower extremities. Her blood pressure on admission was 170/80; it fell to 135/80 on discharge. Her course was febrile; the leucocyte count was high; the erythrocyte sedimentation rate was elevated. A cardiac roentgenogram showed tremendous enlargement involving all of the chambers. During the remainder of her life she always displayed a similar cardiac silhouette. After nine months of bed rest, digitalis, and diuretics, she improved somewhat and was discharged to the clinic in December, 1933, on a maintenance dose of 0.3 Gm. of whole leaf digitalis daily.

From this time on her cardiac reserve was greatly diminished, and she spent a large part of each day in bed. She was admitted to the hospital in January, 1935, for an alveolar abscess, and again in August of the same year for a recurrence of pains in the joints, but on neither of these occasions was the cardiac status much changed. The same was true of her course in the clinic during the next two years.

On the evening of Dec. 29, 1937, after a hearty meal, the patient died suddenly while preparing to retire. She was 33 years old. No necropsy was obtained.

CASE 3.—S. Y., a white female schoolteacher, had severe growing pains between the ages of 9 and 12, and an attack of chorea at 12 years, which lasted for several

months. At 15 years a heart murmur was discovered, but, as she had no symptoms, her physical activity was not curtailed.

In 1910, at the age of 29, she was first seen by Dr. Joseph H. Bainton and remained under his care until 1935. His records reveal that there were no cardiac symptoms in 1910. There were a presystolic thrill and murmur limited to the apical region, but no enlargement of the heart. The second aortic and pulmonic sounds were of good quality and of equal intensity. The rhythm was regular; the rate was 68 per minute; and the blood pressure was 105/84.

The following year she had mild articular pains on several occasions, usually associated with or immediately following an upper respiratory infection. Palpitation on effort was initially noted at this time, but the pulse was always regular. The patient was digitalized, but the drug was discontinued when it proved ineffectual for this symptom.

In 1916, at the age of 35, a blood-streaked sputum was produced on several occasions. In 1917 a severe attack of follicular tonsillitis occurred and was followed by mild pains in the joints which persisted for several months. During this time there was no fever.

In the period from 1917 to February, 1923, there were no joint pains, although occasionally she complained of palpitation and had hemoptysis on a few occasions. In 1923 the patient had a prolonged period of hemoptysis accompanied by pain in the precordial area. This episode was considered a left lower lobe pulmonary infarct. Immediately after this episode, she developed signs and symptoms of heart failure.

Physical examination at this time revealed no change in the cardiac findings, except that the rhythm was irregular due to many premature contractions, the exact origin of which was not determined. There were moist râles at both lung bases, but no other objective findings of congestive heart failure. Digitalis was again administered, this time with success, and she was kept on a daily maintenance dose of 0.1 Gm. whole leaf digitalis.

During an attack of acute bronchitis in February, 1924, at the age of 43, auricular fibrillation, proved by an electrocardiogram (Fig. 1*C*) began and persisted for the remainder of her life. Except for the arrhythmia, the electrocardiogram showed no other alteration from the normal. No signs of heart failure developed with this change in rhythm, presumably because she was fully digitalized. Her blood pressure was normal.

Three months after the onset of auricular fibrillation, an embolus lodged in the right popliteal artery, but recovery was rapid. Nothing of importance occurred until January, 1928, four years after the onset of auricular fibrillation, when another embolus lodged in the left popliteal artery, but again adequate collateral circulation developed and there was no residual vascular insufficiency.

Late in 1930, the patient's cardiac reserve began to decrease considerably. An orthodiagram at this time showed a moderately enlarged heart, the actual transverse diameter being 14 cm., while the predicted diameter, based on the Hodges-Eyster formulas, was 11.3 cm. The left auricle was seen to be enlarged in the lateral and oblique views. The heart continued to increase in size, and on the last orthodiagram in 1936 the transverse diameter measured 15.7 cm. In November, 1930, she developed classical sings of infarction of the lower lobe of the left lung. From then until 1935, she had moderate dyspnea on effort, and during most of the time râles were heard at both pulmonary bases. During this interval the blood pressure rose steadily to hypertensive levels, so that by the end of 1935 the systolic pressure was over 200, and the diastolic, over 100 mm. of mercury.

From 1935 to the time of her death, the patient was under the care of Dr. Clarence E. de la Chapelle and one of us. In 1937 she took a sabbatical leave from her teaching duties for the first time. In October of that year, severe congestive heart failure developed after unusual physical exertion. This responded partially to rest in bed and ammonium chloride, so that she was able to be up and about the house. On the day of her death, Feb. 1, 1938, she awoke feeling well and made a visit to the school at which she taught. Upon leaving the school and while walking to a bus, she suddenly became dyspneic and cyanotic. She was taken home by taxicab, and died a few minutes after arriving. She was not seen by a physician immediately before death, and no necropsy was performed. It was surmised that a pulmonary embolus was the cause of death.

TABLE I

SUMMARY OF CASES

	CASE 1 (S. A.)		CASE 2 (J. A.)		CASE 3 (S. Y.)	
	YEAR	AGE IN YEARS	YEAR	AGE IN YEARS	YEAR	AGE IN YEARS
First rheumatic manifestation	1913	23	1912	7	1890	9
Discovery of cardiac disease	1905	15	1914	9	1896	15
First diminution of cardiac reserve	1914	24	1914	9	1911	30
Onset or discovery of auricular fibrillation	1914	24	1921	17	1924	43
First episode of congestive heart failure	1914	24	1916	11	1923	42
Subsequent failures	1914-18*	24-28	1921	17		
	1933	43				
	1934	44	1933	29	1937	56
Death	1935	45	1937	33	1938	57
Cause of death	Hemorrhagic infarction of the ileum		Unknown (sudden)		Unknown (sudden)	
Duration of life after discovery of auricular fibrillation	21 years		16 years		14 years	
Years of employment after discovery of auricular fibrillation (cardiac reserve good)	15 years		12 years		13 years	
Final cardiac diagnosis†	(a) Rheumatic inactive.		(a) Rheumatic inactive.		(a) Rheumatic inactive. Hypertension.	
	(b) Enlarged heart with massive left auricular hypertrophy and dilatation, mitral stenosis, mitral insufficiency.		(b) Enlarged heart, mitral stenosis, mitral insufficiency, aortic insufficiency.		(b) Enlarged heart, mitral stenosis, mitral insufficiency.	
	(c) Auricular fibrillation		(c) Auricular fibrillation		(c) Auricular fibrillation	
	(d) III D		(d) III D		(d) III D	

*In chronic heart failure with remissions for the four-year period indicated.

†In accordance with *The Nomenclature and Criteria for the Diagnosis of Diseases of the Heart*, ed. 4.

SUMMARY AND CONCLUSIONS

Three cases of rheumatic mitral stenosis complicated by auricular fibrillation were observed for periods of fourteen, sixteen, and twenty-one years, respectively. While under observation, one patient developed aortic insufficiency, and another, hypertension.

Although congestive heart failure contributed to the death of each, it was not the primary cause. In one, death was caused by gangrene of the ileum, although a mesenteric thrombus or embolus could not be demonstrated at necropsy. In the remaining two, death was sudden, suggesting an embolic accident. One case had four embolic accidents during life, two to the lungs and two to the lower extremities, exclusive of the final episode. The other two cases had no clinical evidence of embolization, except terminally.

All three had long periods, twelve, thirteen, and fifteen years, respectively, during which they were gainfully employed despite their auricular fibrillation. Two of them were constantly under the influence of digitalis, while in the other case this drug was taken irregularly.

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AURICULAR AND VENTRICULAR PERICARDIAL FRICTIONS

P. Cossio, M.D., I. Berconsky, M.D., and R. G. Dambrosi, M.D.
Buenos Aires, Argentina

A STUDY of heart sounds and murmurs was made by means of graphical registration excluding the pericardial frictions (Cossio,[1] Leblanc,[2] Orías and Braun Menendez,[3] Calo,[4] Pazzanese[5]). In one case (Caló[4]) there is a questionable record of pericardial frictions because of the time and low frequency of the vibrations, since the auscultation was negative and necropsy showed adhesive pericarditis. In the consulted bibliography another doubtful record of pericardial frictions was found (Dassen and Vitale[6]) and was due to the absence of well-differentiated vibration within a defective base line.

Two conditions may have caused the failure of graphical registration of pericardial frictions: (1) the rarity and (2) the incapacity of the devices in use.

There is no doubt that the second condition is the more essential in the failure of registration for other phenomena of much more exceptional observation, such as the telesystolic and protodiastolic adhesive pericarditis clicks, were recorded.

The use of an electrophonocardiographic unity of broad yield, concerning both frequency and intensity, showed one of us (P. C.) in a routine examination of the private practice, the unmistakable record of a pericardial friction, and, as the analysis proved some facts classically accepted and revealed some others, further observation was undertaken.

Although the number of cases is small, the uniformity of the results justifies following commentaries and conclusions.

CASE REPORTS

Case 1.—A man, aged 63, old dietetically compensated diabetic, under the care of one of us for a year and a half, had angina pectoris spontaneously or when disturbed by the slightest emotion. With large doses of trinitrine (he had masticated about 3,000 pills) T_2 and T_3 were permanently negative. On April 18, 1941, in the early morning, there was a very severe midsternal pain; trinitrine was ineffective, and three 0.02 gr. morphium injections were required to stop the pain; the following day there were slight fever and a to-and-fro pericardial friction.

A simultaneous electrocardiogram and phonocardiogram (the first in three limbs derivations and IVF, the second in the four foci of auscultation using different filtration) showed electric alterations of a recent myocardial infarction (anterior type)

From the Cardiological Department of Buenos Aires Medical School (Semiological Institute, Prof. T. Padilla.)
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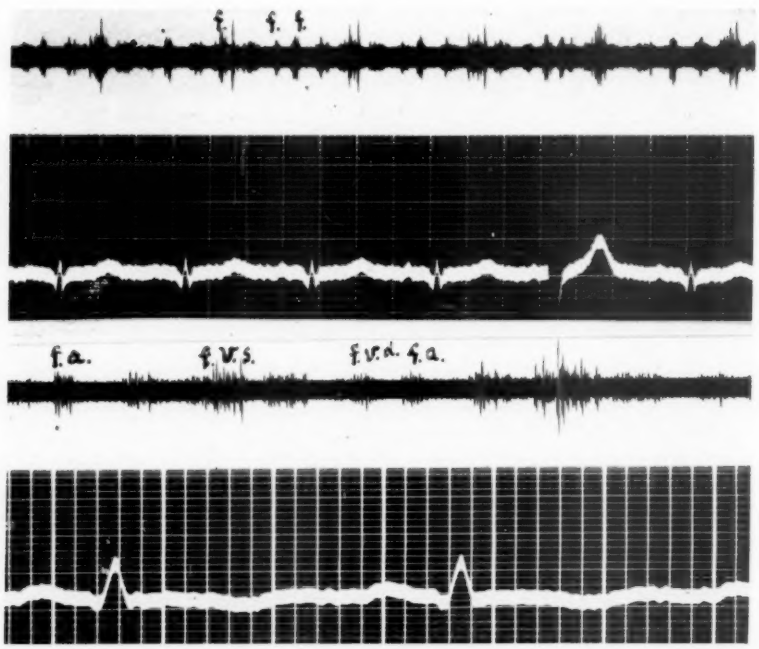

Fig. 1.—Stethoelectrocardiograms recorded at slow and high speed showing auricular (*f.a.*) ventricular systolic (*f.v.s.*), ventricular diastolic (*f.v.d.*) pericardial frictions of harmonical high pitch.

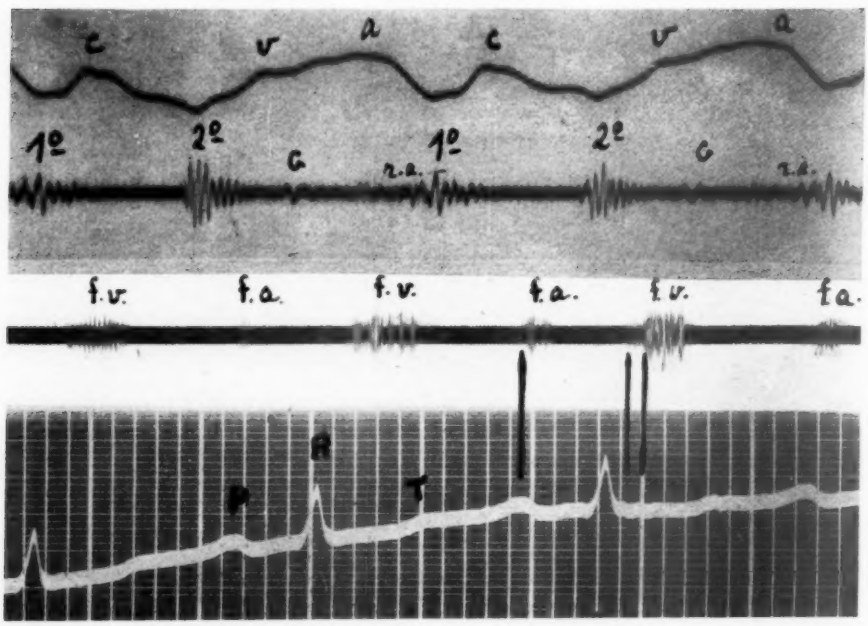

Fig. 2.—(Upper) Phlebostethogram, with accurate filtering for low pitch showing protodiastolic gallop rhythm and auricular sound before Brightical pericarditis. (Down) Stethoelectrocardiogram, auricular (*f.a.*) and systolic ventricular (*f.v.*) pericardial friction of harmonical high pitch.

and a series of more or less homogeneous high-pitched vibrations, exactly in the middle of systole, and protodiastole and presystole at the height of the P wave (Fig. 1).

CASE 2.—A man, aged 49, a physician, with chronic glomerulonephritis and hypertension and under the care of one of us (P. C.), had paroxysms of left ventricular failure and chronical uremia. On June 24, 1941, there was a Bright pericarditis with pericardial frictions rubs in to and fro, which could be heard and felt but with a much more intensive systolic element.

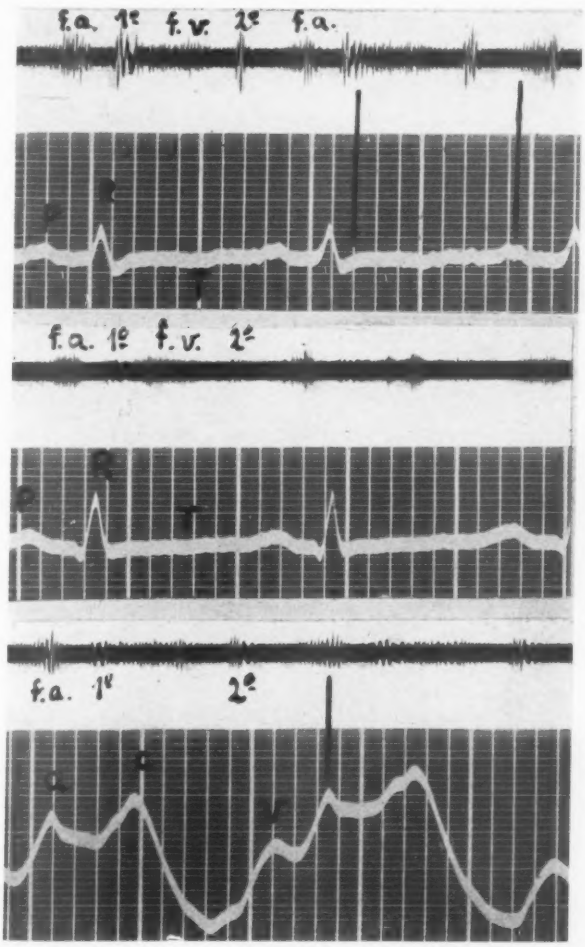

Fig. 3.—Stethoelectrophlebogram with different filterings showing auricular (*f.a.*) and ventricular systolic (*f.v.*) pericardial friction with harmonical high pitch.

The electrocardiogram of the three limb derivations and IVF, simultaneously recorded with the phonocardiogram of the four foci of auscultation with different filtration, showed left axis deviation with opponent S-T and T, and two groups of somewhat homogeneous high-pitched vibrations (the more important was in the middle systolic; the other, just at the height of the P wave) (Fig. 2).

CASE 3.—A woman, aged 45 years, with splenic anemia, was a patient at the Semiology Institute. A few days after the splenicthemy, there were polyserositis

with negative T waves in all derivations and a to-and-fro pericardial friction.

The phonocardiogram of the four foci of auscultation with different filtrations simultaneously registered with a derivation of the electrocardiogram or phlebogram showed, besides the fundamental heart noises, two groups of homogeneous vibrations; the first was systolic, longer, and more intense than the other group, which was smaller, beginning just at the height of the P wave and in the ascending branch of *a*.

CASE 4.—A man, aged 30 years, had polycystic kidney hypertension and uremia presenting an always marked protodiastolic gallop rhythm, often registered. There was a to-and-fro pericardial friction, by Bright pericarditis.

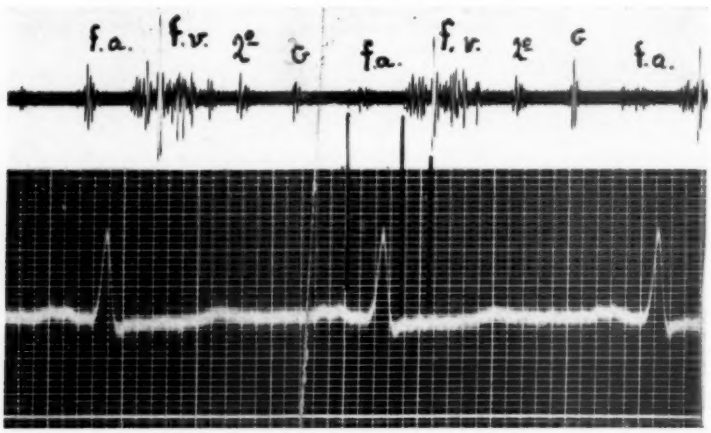

Fig. 4.—Stethoelectrocardiogram showing the auricular (*f.a.*) and systolic ventricular (*f.v.*) pericardial friction. *2°*: second sound, *G*: gallop rhythm.

The phonoelectrocardiogram recorded by Dr. Campana, showed, besides the fundamental heart sounds and the protodiastolic gallop rhythm, evidence of two groups of somewhat homogeneous vibrations; the systolic one was lower and more intense, and the other was shorter and smaller, beginning just at the summit of the P wave (Fig. 4).

COMMENTS

Cullin[7] (1824) described the pericardial friction sound; he compared it to a new leather rub *(craquement de cuir neuf)* and attributed it to the slipping of the abnormally dry pericardium.

Latham[8] (1826) explains that the pericardiac friction sometimes does not show this acoustic character, seeming better a murmur because of friction of the unpolished pericardium.

Stokes[9] (1833) revises these and other acoustic modalities of the friction sounds and shows, as an important characteristic, its variations in the postural changes.

Hope[10] (1839) adds, as a fundamental characteristic, that the pericardiac friction is frequently a double to-and-fro noise, the first more intense than the second, in correspondence with the movements of the organ backward and forward within the pericardium during the cardiac cycle; but sometimes the noise may be only one, and then, systolic.

Pennock[11] (1846) fixed and completed this knowledge verifying that the to-and-fro noises could be formed by three or four noises according with the pericardial friction produced by the consecutive and independent systolic and diastolic auricular and ventricular movements.

Sansom[12] (1850) states that the pressure exerted by the stethoscope on the precordium exaggerates the friction noises increasing the pericardial contact, but Walshe[13] (1853) proves that it happens when the stethoscope pressure is adequate, for its excessive increase abolishes the pericardial rub explained by Friedreich[14] (1873) as the result of the impairment of pericardial slipping.

The stethographic record of pericardial frictions shows the source of the to-and-fro noise and explains the intensity variations by the stethoscope's pressure.

The to-and-fro noise was proved to be double more frequently than triple. It happens that the most intensive and longer is always systolic, coincidently with the ventricular systole since it is a ventricular systolic friction. The other, or the remaining two, are diastolic; when only one is present, it is synchronic with the auricular systole, thus being an auricular friction; when there are two diastolic rubs, one is auricular and the other coincides with the rapid inflow, giving rise to a ventricular diastolic friction.

The incidence of the so-called ventricular frictions during the middle of the systole or maximum ejection phase and the protodiastole or rapid inflow shows that the pericardial rubs are in relationship to the maximal changes in volume and position of the ventricles with the consequent friction of the pericardium which covers them.

The verification that the so-called auricular friction noise coincides with the height of the auricular systole does not require more explanation than that the rubs are caused by the friction of the auricular pericardium and not the friction of the ventricular pericardium during the distention of these chambers by the blood coming from the auricle.

The verification that the to-and-fro noise of the auricular pericardial friction depends on the auricular systole suggests that, according to its production's time during the great silence, the conditions of the auricular-ventricular conduction can be deducted by the auscultation, as reported by Vedoya[15] in an active rheumatic carditis with delayed auricular-ventricular conduction where the auricular friction was produced in the mid-diastole instead of the presystole.

The increase and disappearing of the friction of the noises by the stethoscope's pressure changes are explained by the graphic record.

The graphic registration of pericardiac frictions with different filtering showed them as acoustic phenomena composed of vibrations of different frequencies—some slow and others fast—generally with overtones taking more sound characteristics rather than noises, in opposition to the other cardiac acoustic phenomena.

The frequency of the stethoscope with the open bell is given by the lengthening of the skin enclosed within the stethoscope's edges—the more the lengthening the higher the frequency and vice versa. The lengthening depends upon the pressures exerted on the skin; the increase of the stethoscope's pressure increases the frequency (Rappaport and Sprague[16]). But further investigations (Cossio and Viale del Carril[17]) showed that the stethoscope's pressure (open bell) modifies not only frequency but amplification. In the progressive increase of pressure, initially there is more amplification with further damping.

Both stethoacoustic principles in connection with the pre-eminent high-pitched pericardial frictions help us to explain their changes, first *waxing* and then *waning* by a greater pressure of the stethoscope against the chest, without any relationship with thoracic deformations giving rise first to more contact and afterward to immobility of the pericardium.

The stethoscope pressing gently on the chest has a lower frequency than the prevailing pitch of the pericardial frictions, failing the transmission to the ear, aside from the masking produced by the predominating lower pitches upon the higher ones.

If the stethoscope exerts more pressure, its own frequency increases and picks up the friction noises; the transmission is better and thus the hearing improves not only because of a better transmission but also because of an inversely acting interference masking as a result of the pre-eminence of the higher pitches as compared with the lower ones.

If the stethoscope's pressure overlaps a critical level, the stethoscope's damping appears quickly, the transmission vanishes, and the pericardial frictions are barely heard or even are inaudible.

SUMMARY AND CONCLUSIONS

1. The graphic registration with different filtering of the pericardial friction rubs shows that it is an acoustic phenomenon more or less harmonic, and in which the relative high pitches prevail.

2. The acoustical characteristic so-called to-and-fro noise can be double or triple. It is more frequently double, the true to-and-fro. Of the two noises, the more intensive takes place during the ventricular systole (ventricular systolic friction); the other noise, the less intensive, is diastolic and is produced during the auricular systole because of the slipping of the pericardium covering these cavities (auricular friction). Less frequently it is triple; the most intensive noise is always systolic (ventricular systolic friction) and the other two are diastolic [one is the auricular friction, and the other is produced during the rapid inflow (ventricular diastolic friction)].

3. The primary waxing and consequently fainting or disappearing of the pericardial friction rub by the progressive increase of the stethoscope's pressure are explained by means of the frequency changes and damping of the stethoscope itself and not by thoracic deformation with more or less pericardial slipping.

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THE EFFECT OF HIGH ALTITUDE AND REBREATHING ON THE DURATION OF ELECTRICAL SYSTOLE IN MAN

M. S. White, M.D., C. E. Kossmann, M.D., and I. Ershler, M.D.
Randolph Field, Texas

OF THE numerous studies on the effect of anoxia on the human electrocardiogram, few make reference to alterations in the duration of electrical systole (Q-T interval). Greene and Gilbert[1] found the "R-T interval" reduced in rebreathing experiments, but admitted that the measurements were difficult to make in many of their curves. Doetsch,[2] using a low-pressure chamber, measured the duration of the "P-T interval" on the ground and at a simulated altitude of 6,000 meters (19,685 feet). Obviously, this interval included a measurement of the auriculoventricular conduction time. In twenty normal subjects who were studied in the sitting position, the "P-T interval" remained the same in two, but was reduced in all the others from 0.01 to 0.12 second. The average reduction for the whole group was 0.031 second. In none of the work on the anoxemia test for coronary insufficiency[3-6] is reference made to the duration of electrical systole.

For the purpose of ascertaining whether there are any alterations in the relation of electrical systole to cycle length during anoxic anoxia, six experiments were performed. All of the subjects were soldiers without a history of, or physical evidence of, heart disease. The thoracic roentgenogram was normal in every case. Records were made with an amplifier type of instrument.* In the experiments done during flight, the subjects were sitting; in those done on the rebreather, the subjects were recumbent.

Experiment I

The standard leads and Lead IVF were recorded on seventeen subjects during actual flights[10] in army transports and bombers to a height of 20,000 feet. Ascent to the highest altitude was made in one to two hours; return to the ground was made in approximately one-half hour. The heart rates, the Q-T intervals, and the systolic indices of Bazett ($K = \frac{Q\text{-}T}{\sqrt{R\text{-}R}}$) were ascertained from the curves recorded on the ground prior to flight, at increments of 5,000 feet during flight, at

From the Department of Aviation Medicine, School of Aviation Medicine, Army Air Forces, Randolph Field, Texas.

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*General Electric, Model B, electrocardiograph.

TABLE I

EFFECT OF ASCENT IN ONE TO TWO HOURS TO 20,000 FEET ON HEART RATE, Q-T INTERVAL, AND SYSTOLIC INDEX IN SEVENTEEN NORMAL SUBJECTS

ALTITUDE (FEET)	RATE PER MINUTE					Q-T INTERVAL IN SECONDS					Q-T / $\sqrt{\text{R-R}}$				
	MIN.	MAX.	MEAN	STANDARD DEVIATION	COEFICIENT OF VARIATION	MIN.	MAX.	MEAN	STANDARD DEVIATION	COEFICIENT OF VARIATION	MIN.	MAX.	MEAN	STANDARD DEVIATION	COEFICIENT OF VARIATION
Ground	59	92	77.6	11.8	15.6	0.30	0.35	0.324	0.013	4.0	0.326	0.397	0.3676	0.0198	5.4
5,000	66	100	81.7	8.3	10.2	0.30	0.34	0.321	0.012	3.7	0.355	0.400	0.3735	0.0131	3.5
10,000	64	100	83.5	10.6	12.7	0.30	0.34	0.322	0.013	4.0	0.351	0.403	0.3777	0.0147	3.9
15,000	71	115	87.7	13.5	15.4	0.28	0.34	0.321	0.014	4.4	0.351	0.444	0.3870	0.0211	5.5
17,500	65	125	92.3	14.8	16.0	0.27	0.36	0.318	0.022	6.9	0.356	0.413	0.3899	0.0168	4.3
20,000*	69	115	91.3	13.0	14.2	0.29	0.34	0.318	0.015	4.7	0.360	0.423	0.3897	0.0178	4.6
20,000 with 100% oxygen*	48	103	65.2	13.8	21.2	0.30	0.41	0.356	0.029	8.1	0.365	0.394	0.3711	0.0154	4.1
Ground*	56	94	71.0	10.7	15.1	0.30	0.38	0.346	0.022	6.4	0.340	0.424	0.3740	0.0193	5.2

*Fifteen subjects.

17,500 feet, at 20,000 feet before and after breathing pure oxygen, and again on return to the ground.* In obtaining these values, an average of at least five complexes and cycles was used in each lead, and the average of all four leads was calculated for each subject.

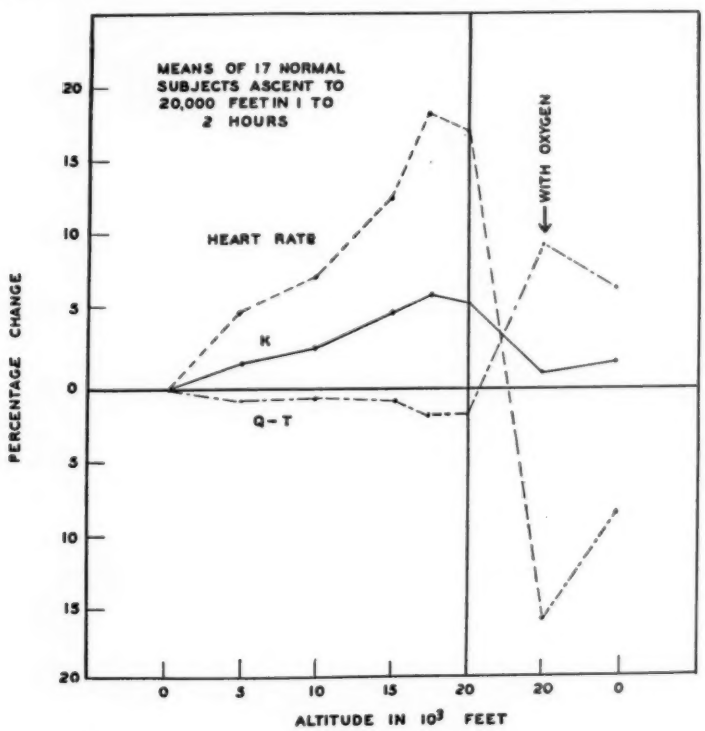

Fig. 1.

The means, standard deviations, and coefficients of variation for these measurements and for the calculated systolic indices were ascertained from the curves which were recorded at the various altitudes (Table I). These values were plotted in terms of the percentage change of the variables mentioned, with relation to the altitude in thousands of feet (Fig. 1). Observations at 20,000 feet, without oxygen, when compared to those made on the ground, showed a mean increase in pulse rate of 17.7 per cent, a mean decrease in the Q-T interval of 1.9 per cent, and a mean increase in the systolic index (K in figure) of 6.0 per cent. The difference between the mean of the systolic index calculated at ground level, and the mean of this index calculated at 20,000 feet, when divided by the standard error of this difference, gave a value of 3.1. This was interpreted to mean that the difference between the true means was reliable and probably greater than zero.

The average pulse rate decreased slightly at 20,000 feet, compared with what it was at 17,500 feet (Fig. 1). It will also be noted that

*Elevation at Randolph Field, 752 feet.

there was a sharp decrease of the pulse rate and an increase of the Q-T interval, as compared to the control levels, when oxygen was given at 20,000 feet. These did not return to normal even after landing, sixteen to fifty-six minutes later. However, in both instances the systolic index returned approximately to normal. Adequate explanations for these phenomena are at present lacking.

The individual records revealed that only one subject showed no change in the systolic index, while sixteen showed an increase. The greatest increase in this measurement at 20,000 feet, as compared with its value at ground level, was 0.045.

To summarize, in flight up to 20,000 feet the Q-T interval does not decrease in proportion to the increase in heart rate, with a consequent increase in the ratio: systole divided by the square root of the cycle length.

Experiment II

We wished to know whether electrical systole would change during flight if the pulse rate remained the same, or approximately the same. These conditions were created in sixteen normal subjects who were slowly flown up to 15,000 feet in approximately one and one-half hours, and maintained at that altitude for two hours. On ascent, the average pulse rate and the average Q-T interval remained practically constant. As the level was maintained at 15,000 feet, the pulse rate of the group gradually decreased and the length of electrical systole gradually increased, but the systolic index was unchanged. This experiment is not strictly comparable with the first, principally because of the lower altitude attained, but it does indicate that, up to 15,000 feet, provided there is no important change in pulse rate, the systolic index will remain constant.

Experiment III

The experiments were repeated with a modified rebreather designed by Major N. W. White, in which the utilized oxygen was replaced by nitrogen, and the carbon dioxide absorbed. In fourteen subjects, the four leads were recorded and measured as before, and the oxygen saturation of the ear blood ascertained by means of the photocell oximeter of Millikan.[16] The same statistical constants were calculated, and the results were plotted as shown in Fig. 2. The Q-T interval, when the oxygen saturation of the ear blood was between 80 per cent and 77 per cent, was reduced 7.6 per cent, as compared to the control value. The pulse rate was increased 20.9 per cent; the systolic index was increased 4.5 per cent; and the fourth variable which could be ascertained, namely, the respiratory volume in liters per minute, corrected for dry gas at 0° C. and 760 mm. Hg, was increased 45 per cent. Compared to the altitude experiments, Q-T was reduced more than it was during flight, but the systolic index increased. In this instance, the increase was not statistically significant.

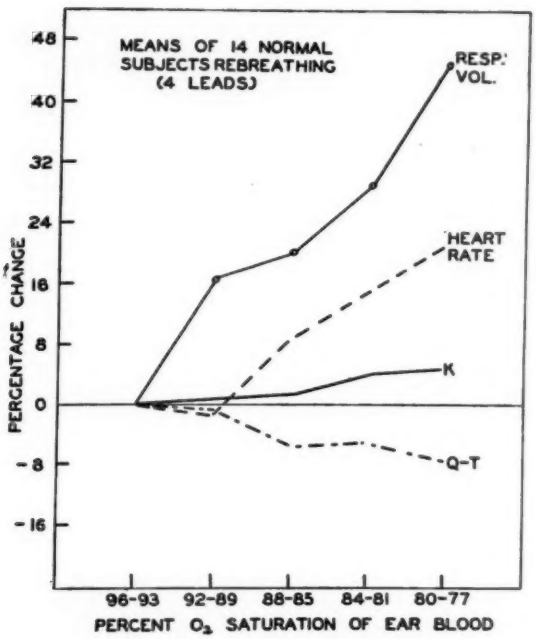
MEANS OF 14 NORMAL SUBJECTS REBREATHING (4 LEADS)
RESP. VOL.
HEART RATE
K
Q-T
PERCENTAGE CHANGE
48
40
32
24
16
8
0
-8
-16
96-93
92-89
88-85
84-81
80-77
PERCENT O2 SATURATION OF EAR BLOOD

Fig. 2

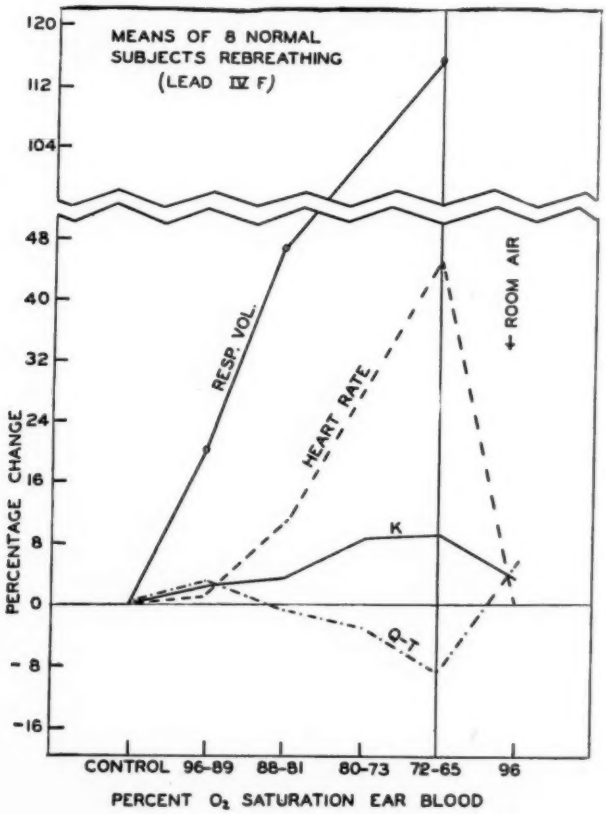
MEANS OF 8 NORMAL SUBJECTS REBREATHING (LEAD IV F)
120
112
104
48
40
32
24
16
8
0
-8
-16
RESP. VOL.
HEART RATE
K
Q-T
+ ROOM AIR
PERCENTAGE CHANGE
CONTROL
96-89
88-81
80-73
72-65
96
PERCENT O2 SATURATION EAR BLOOD

Fig. 3.

Experiment IV

In the previous experiment the oxygen saturation of the blood was reduced to a level between 80 per cent and 77 per cent, which is comparable to an altitude of approximately 15,000 to 16,000 feet. In another group of eight subjects, the oxygen saturation was reduced to 65 per cent (approximate, calculated altitude, 21,280 feet) while lead IVF was being recorded. The results are shown in Fig. 3. The data on oxygen saturation are grouped rather grossly because a greater accuracy for the method of Millikan, especially at the lower saturations, is not claimed. The results bore out those obtained in flight and in the previous rebreathing experiment in which four leads were recorded. The average heart rate was increased 44.8 per cent; the average Q-T interval was reduced 9.0 per cent; and the average systolic index increased by a statistically significant 8.7 per cent. The respiratory volume, also measured in this instance, and corrected for dry air at 0° C. and 760 mm. Hg, showed an increase of 117 per cent.

The change in these variables was greater than during flight. The speed with which anoxia was induced was apparently the important reason for this difference. By rebreathing, an oxygen saturation of 65 per cent was attained in less than twenty-five minutes.

Experiment V

In all of the experiments described thus far, different normal subjects were used. For the purpose of controlling this variable, nine of the normal subjects, who had been previously studied on the rebreather with the four leads, were taken on a flight to 20,000 feet in approximately one and one-half to two hours. The results in this group were precisely the same as those obtained with the seventeen normal subjects in Experiment I.

Experiment VI

The effect of an increase in the pulse rate on the systolic index was studied in normal subjects on the ground. In order to increase the pulse rate, the use of drugs such as atropine and the nitrites was considered, but it was felt that their side actions made them undesirable for the purposes of this experiment. Judging from the literature, the results of exercise on the systolic index have been variable and confusing. Bazett[8] calculated the systolic index in the electrocardiograms of three subjects who had been exercised by Lewis and Cotton. In two, the immediate change after exercise was a decrease, with a subsequent increase as the subject rested. Barker, Shrader, and Ronzoni[9] did an exercise test on four subjects, which consisted of running up and down stairs until shortness of breath and fatigue were pronounced. This exercise was sufficient to reduce the pH and the carbon dioxide combining power of the blood, and to increase the lactic acid content. In

TABLE II

THE EFFECT OF RAPIDITY OF THE PULSE RATE INDUCED BY EXERCISE ON THE SYSTOLIC INDEX IN TEN NORMAL SUBJECTS

SUBJECT	RESTING			IMMEDIATELY AFTER EXERCISE			TWO MINUTES AFTER EXERCISE		
	Q-T	RATE	$\frac{Q\text{-}T}{\sqrt{R\text{-}R}}$	Q-T	RATE	$\frac{Q\text{-}T}{\sqrt{R\text{-}R}}$	Q-T	RATE	$\frac{Q\text{-}T}{\sqrt{R\text{-}R}}$
F-1	0.40	62	0.408	0.32	90	0.391	0.42	52	0.390
F-2	0.32	104	0.421	0.28	121	0.378	0.30	112	0.410
F-3	0.36	81	0.419	0.32	100	0.413	0.36	70	0.388
F-4	0.36	66	0.377	0.30	95	0.378	0.34	80	0.393
F-5	0.35	75	0.391	0.28	93	0.348	0.34	80	0.393
F-6	0.37	58	0.362	0.32	85	0.380	0.38	61	0.384
F-7	0.37	68	0.394	0.28	111	0.381	0.34	79	0.390
F-8	0.32	78	0.364	0.30	91	0.369	0.32	75	0.358
F-9	0.36	81	0.419	0.32	100	0.413	0.34	81	0.395
F-10	0.36	75	0.403	0.32	95	0.403	0.36	81	0.419
Means	0.357	74.8	0.3958	0.304	98.1	0.3854	0.350	77.1	0.3920
Percentage deviation from control				-14.8	+31.1	-2.6	-2.0	+3.1	-1.0

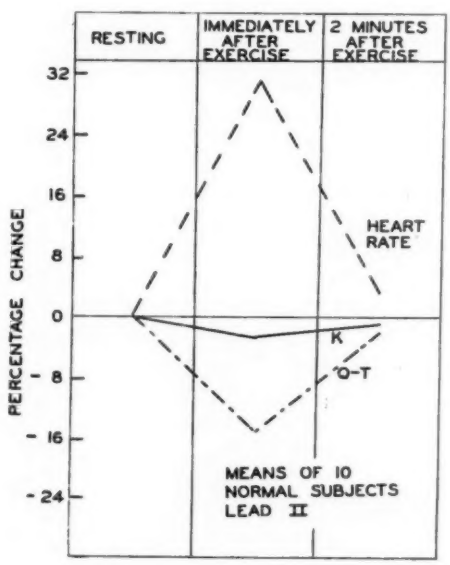

Fig. 4.

all four the systolic index was slightly increased immediately after exercise, and continued to be increased for an unspecified period after the exercise had been completed. Our intention was not to induce acidosis by exercise, but simply to produce an increase in the pulse rate. For this purpose, an exercise test, which consisted of hopping approximately one inch from the floor on one foot a hundred times in forty to fifty seconds, was done. With the subject recumbent, Lead II of the electrocardiogram was recorded as a control immediately after exercise, and again two minutes later. From the results shown in Table II and Fig. 4, it is clear that the average systolic index was immediately decreased,

and returned almost to normal two minutes after the exercise had been completed. Of the individual records, three showed a slightly increased index immediately after exercise; one was the same as the control; and the remaining six showed considerable decreases. Two minutes after exercise, four of the records showed a systolic index somewhat above the control value; the remaining six showed indices below the control value.

DISCUSSION

During anoxia, some change, probably chemical, is taking place in the muscle of the heart, and this opposes the shortening of the electrical recovery process that ordinarily occurs when the heart rate is increased. It is known that one of the ions in the blood serum which has a considerable effect on the duration of electrical systole is calcium. Any reduction of this circulating ion will result in a prolongation of the Q-T interval.[17, 18] Since ventilation increases greatly during anoxia, it is possible that the ionized calcium is reduced by hyperventilation. This theory becomes more attractive when it is recalled that the low T waves during anoxia[1, 10] are similar to those which occur with alkalosis.[9] Data on the serum calcium at high altitudes are, however, conflicting. Goralewski[11] demonstrated slight decreases in blood calcium when oxygen deficiency was induced at normal atmospheric pressures. McFarland,[12] with a similar technique, found little change, either in normal or neurotic subjects, when an altitude of 18,000 feet was simulated. A conclusion on the importance of calcium does not seem possible without further investigation.

In Experiment I (Table I) the average systolic index of the seventeen men before flight was 0.3676. In only one instance was it greater than 0.392, which was the maximum observed by Bazett in fifteen normal men. In Experiment IV (Table II) the average systolic index of the ten men before exercise was 0.3958, and in six it was more than 0.392. The only difference in procedure in the two experiments was the posture of the subjects. In the former they were sitting; in the latter they were recumbent.

Cheer and Li[19] found that a change in posture made a difference in the value of K. In seventy-five recumbent men the average value was 0.3741, and, in thirty-four other sitting men, it was 0.3698. This difference was not statistically significant. In Experiment III, control electrocardiograms were recorded on six subjects in both positions. When they were sitting, the average index was 0.3880, and when they were recumbent it was 0.3826. In two of the six it was shorter in the sitting posture.

The effect of different postures seems insufficient to explain the discrepancy between Experiments I and VI. A more probable explanation is inaccuracy of the time marker. A stroboscopic check on the timer indicated that it was probably operating incorrectly during Experiment

I. Although this makes the absolute measurements in this experiment unreliable, the relative changes are valid.

Systolic indices in excess of 0.392 have often been noted in normal male subjects by one of us (C. E. K.). The straight line regression formula calculated by Adams[13] from his data on normal subjects persistently gave a longer duration for Q-T than similar formulae calculated from the data of Cheer and Li[19] and of Fridericia.[14] Larsen and Skúlason[15] have confirmed the validity of Adams' formula. The discrepancy between these two groups of investigations also seems to be attributable to failure of the earlier workers to check the timing mechanism of their recording instruments.[13, 15]

CONCLUSIONS

1. During anoxic anoxia induced by rebreathing or by flight into high altitudes, the ratio of the length of electrical systole to the square root of the cycle length is increased.

2. This increase occurs only when the pulse rate is increased, which means that it is the result principally of shortening of the cycle length without the expected shortening of the duration of systole.

3. With exercise of moderate amount, with the subject on the ground, the systolic index is, on the average, shorter immediately after exercise.

4. The conclusion reached is that anoxia opposes in some way those factors which, under normal conditions of oxygen tension, cause a decrease in length of electrical systole as the cycle length shortens.

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A STUDY OF THE ANALEPTIC VALUE OF CERTAIN DRUGS IN THE TREATMENT OF QUINIDINE DEPRESSION

S. A. Weisman, M.D.
Minneapolis, Minn.

PATIENTS who have been taking quinidine have occasionally died suddenly without apparent cause. Even post-mortem examination often shows no cause for such deaths. Death may have been the result of auricular and ventricular standstill, or of vascular or respiratory collapse.

It is known that quinidine, when given to dogs intravenously in large doses, causes a marked fall in blood pressure and a slowing of respiration. The blood pressure may continue to fall; the respiration may become very slow and finally cease. The heart, however, may continue to beat for several minutes after respiration ceases (Fig. 1). This confirms the observations of Barker and Levine[16] and of Gordon, Matton, and Levine.[17]

The present study records data on the relative values of ten drugs which are used experimentally as analeptics in varying states of cardiovascular and respiratory depression caused by quinidine.

The drugs were divided into two groups for comparison as to their analeptic value. In Group I were coramine, picrotoxin, metrazol, and caffeine sodium benzoate. In Group II were benzedrine, paredrinol, paredrine, epinephrine, ephedrine, and neosynephrin.

Dogs were anesthetized with pentobarbital sodium, which was given intraperitoneally in doses of 35 mg. per kilogram of body weight. Quinidine was then administered intravenously in doses of varying size; 25 mg. per kilogram and less were considered small doses, and more than 25 mg. per kilogram was considered large. We found that 45 mg. of quinidine per kilogram was a sublethal dose.

From the Department of Medicine and the Department of Pharmacology, University of Minnesota.

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Fig. 1.—Effect of quinidine on the blood pressure. Upper tracing, resp'ration; lower tracing, blood pressure. Time marking, below, in seconds.

GROUP I

Coramine

(pyridine betacarbonic acid diethylamide, 25 per cent solution)

Killian[1, 2] and Barlow[3] report that coramine will overcome light narcosis caused in rabbits by paraldehyde and avertin. Maloney and Tatum[4] found coramine rather effective in counteracting the respiratory depressive effects of urethane, chloral hydrate, avertin, and ether, but it had little antidotal action against the barbiturates. Mousel and Essex[5] found coramine without value in treating severe depression caused by pentothal sodium anesthesia in dogs, cats, and rabbits. Clinically, Wood[6] reports definite respiratory benefits from the use of coramine in patients with marked depressive effects caused by avertin or surgical shock. He states that the toxicity of coramine is low, that it can be given intravenously in large doses, and that the dose can be repeated.

Table I gives the results of fourteen of our experiments in which coramine was given as an antidote after small, sublethal doses of quinidine had been given. We found that doses of 0.2 to 0.25 of coramine per kilogram were most effective. Smaller doses were ineffective and larger doses proved toxic.

Maloney,[7] working with cats, found that amounts up to 150 mg. of coramine per kilogram had no demonstrable effect on animals that previously had been given 200 mg. of barbital per kilogram. Larger doses of coramine delayed recovery from the poisoning effects of barbital.

Burnstein and Rovenstine[8] found amounts less than 5 c.c. only slightly effective or entirely ineffective in human beings who were under the effects of anesthetics or hypnotics, and advocated 5 c.c. doses, repeated, if needed, at five- to ten-minute intervals until 25 c.c. had been given. The intravenous route was most effective.

It will be noted that in our experiments the blood pressure always fell immediately after the administration of coramine; this was also shown by Maloney and Tatum[4] and by Mousel and Essex.[5] The blood pressure would tend to return to the previous level in about one minute or more. Sometimes the blood pressure would rise slightly above the previous level (Fig. 2).

Stoland and Ginsberg,[9] working with heart-lung preparations and with intact dogs, found that coramine caused a fall in blood pressure and an increase in coronary flow.

In two of our experiments, when coramine was given after a sublethal dose of quinidine had been administered, the blood pressure continued to fall and the animals died. When smaller doses of quinidine had been administered, causing a fall of blood pressure not below 80 mm. Hg, coramine stimulated the respiratory center, as was manifested by an increase in depth and rate of respiration (Fig. 2). When large or

TABLE I

CORAMINE

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)	BLOOD PRESSURE		DOSE OF CORAMINE (C.C. PER KG.)	BLOOD PRESSURE		RESPIRATION	
			BEFORE QUINIDINE	AFTER QUINIDINE		BEFORE CORAMINE	AFTER CORAMINE	AFTER CORAMINE	BEFORE CORAMINE
1	15.0	40.0	136	20	0.43	20	0 30″—died		
2	16.8	12.0	124	90	0.10	50	30 in 4′ 92 in 38′	25	19
3	10.0	46.0	140	50	0.15	50	40 in 2′ 45″ N.C. in 7′ 15″	19	21
4	16.8	23.8	156	85	0.20	75	60 in 1′ 50″ 80 in 6′		N.C.
5	13.8	43.0	150	42	0.70	42	0 in 6′—died		
6	17.5	23.0	140	70	0.20	70	55 in 1′ 70 in 17′ 30″	14	17
7	18.1	44.0	92	8	0.20	8	0 in 1′ 30″ 20 in 108′		N.C.
8	10.0	40.0	98	6	0.20	6	0 in 1′ 10 in 40′ 15″	16	44
9	10.5	9.5	150	128	0.20	128	122 in 2′ 144 in 17′	14	18
10	9.5	10.0	160	120	0.20	120	114 in 2′ 30″ 120 in 3′ 30″	19	24
11	9.7	10.0	160	130	0.20	120	114 in 4′ 30″ N.C. in 10′	10	11
12	21.5	45.0	142	50	0.20	57	42 in 1′ 54 in 20′	–	–
13	19.3	8.6	140	120	0.30	120	118 in 2′ 0″ (Rose to 130 in 5′)	19	27
14	19.3	45.0	130	56	0.30	56	40 in 10′	18	21

N.C., No change.

sublethal doses of quinidine had been given, causing a marked fall in blood pressure and a slowing of respiration, coramine sometimes added to the depression and proved fatal. Whitehead and Draper[10] found that coramine almost doubled the mortality from an overdose of chloroform in dogs. Peters and Visscher,[11] using a heart-lung preparation, found that coramine produces, instead, dilatation of the heart, with decreased output and efficiency.

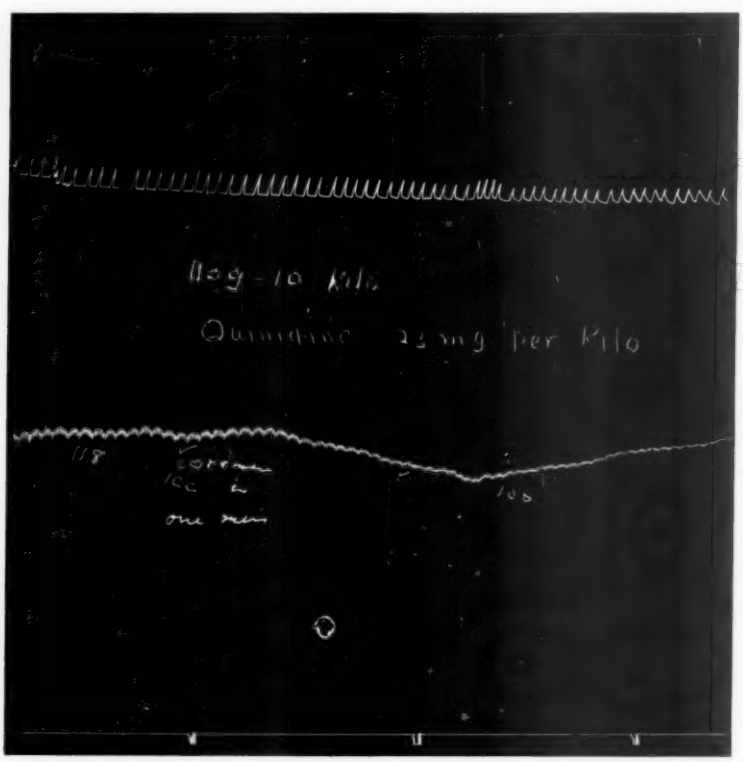


Fig. 2.—Effect of coramine on the blood pressure.

One must bear in mind that investigations made under conditions which differ in even a very slight degree may in all probability produce results that are not in complete harmony.

Picrotoxin

(a substance found in poison fish berries, *Cocculus indicus*)

Maloney, et al.,[12, 13] experimenting with rabbits and dogs, found that picrotoxin, although it stimulated the respiratory mechanism, was definitely effective as an antidote in acute poisoning caused by the longer- and shorter-acting barbiturates.

Rice and Isenberger[14] found that the drug shortened the duration of the respiratory paralysis produced in dogs by intracisternal injections of sodium amytal. Marshall, Walzl, and LeMessuier[15] found that it was

TABLE II

PICROTOXIN

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)	BLOOD PRESSURE		DOSE OF PICROTOXIN (MG. PER KG.)	BLOOD PRESSURE		RESPIRATION	
			BEFORE QUINIDINE	AFTER QUINIDINE		BEFORE PICROTOXIN	AFTER PICROTOXIN	BEFORE PICROTOXIN	AFTER PICROTOXIN
1	17.5	23.0	140	58	3.0	58	62 in 6′		N.C.
2	18.6	10.8	150	90	3.0	100	96 in 2′		N.C.
							100 in 6′		
3	18.6	21.0	140	58	6.0	58	68 in 6′	20	32 in 6′
4	18.6	38.0	150	70	3.0		N.C.	32	36 in 14′
5	18.6	45.0	150	68	6.0		N.C.	18	15 in 12′
6	21.5	45.0	140	48	6.0		N.C.		N.C.
7	10.0	46.0	140	70	3.0	70	78 in 4′	19	20
8	15.9	45.0	100	54	6.0	60	68 in 25′	20	27 in 25′
9	11.6	10.0	180	120	3.0	120	125 in 5′		N.C.
10	11.6	45.0	180	72	3.0	100	95 in 2′		N.C.
							100 in 1′		

N.C., No change.

TABLE III

METRAZOL

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)	BLOOD PRESSURE		DOSE OF METRAZOL (C.C. PER KG.)	BLOOD PRESSURE		RESPIRATION	
			BEFORE QUINIDINE	AFTER QUINIDINE		BEFORE METRAZOL	AFTER METRAZOL	BEFORE METRAZOL	AFTER METRAZOL
1	10.4	10.0	140	88	0.13		N.C. in 7′	52	36
2	10.4	48.0	110	40	0.15	40	36 in 6′	35	24
3	12.0	8.6	140	120	0.2	120	138 in 3′	36	24
4	18.6	10.7	126	95	2.8	95	93 in 3′	26	33
5	12.0	45.0	140	40	0.3	44	43 in 8′	36	30
6	10.4	45.0	140	36	1.5	36	34 in 2′	35	34
							36 in 10′		

N.C., No change.

effective in dogs and cats against overdosage with chlorbutanol, paraldehyde, or "avertin fluid," and that it usually stimulated respiration in anesthetized animals in nonconvulsive doses. In a study of several analeptics, Barlow[3] found it most effective in improving the respiration and circulation in rabbits, and in shortening the usual stages of recovery caused by sublethal doses of pentobarbital, chloral hydrate, and tribromethanol (avertin).

Mousel and Essex[5] found picrotoxin without value in treating the depression caused by minimal lethal doses of pentothal sodium in dogs.

The results of our studies with this drug are shown in Table II. It will be observed that very little analeptic effect was obtained by using this drug after the administration of quinidine. However, when only small doses of quinidine had been used, the administration of picrotoxin did have a slight respiratory stimulating effect. There was no appreciable vascular effect.

Metrazol

(pentamethylene tetrazol)

Barlow[3] found that, in rabbits, metrazol was an effective analeptic against sublethal and lethal doses of pentobarbital, chlorhydrate, and tribromethanol (avertin). He also found that its antidotal effect was in inverse proportion to the depth of the narcosis. No beneficial analeptic effects were obtained by Maloney and Tatum[4] by giving metrazol to rabbits with barbiturate depression. Peters and Visscher[11] found that metrazol produced very little effect on the heart-lung preparation. Barker and Levine[16] found that, in cats, cardiozol (metrazol) had little beneficial effect on the cardiovascular and respiratory depression caused by large doses of quinidine. Larger doses seemed to kill the animal promptly.

Table III shows the results of our study. Three dogs were given very small doses of quinidine, and three were given sublethal doses before the administration of metrazol. In only one case was there a rise in blood pressure, and this dog had received intravenously only 8.6 mg. of quinidine per kilogram, with a fall in blood pressure from 140 to only 120. In all other cases the blood pressure either fell or did not change. Respirations, however, seemed definitely improved.

Caffeine Sodium Benzoate

Gordon, Matton, and Levine,[17] experimenting with cats, found caffeine sodium benzoate very effective in counteracting the depressive effects on respiration caused by large doses of quinidine. They found that about 5 mg. of caffeine sodium benzoate per kilogram, administered about the time when cessation of respiration seemed to be imminent, helped the return to normal breathing, but they found artificial respiration even more effective. However, caffeine sodium benzoate and artificial respiration together were more effective than either alone.

TABLE IV

CAFFEINE SODIUM BENZOATE

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)	BLOOD PRESSURE		DOSE OF CAFFEINE SODIUM BENZOATE (MG. PER KG.)	BLOOD PRESSURE			RESPIRATION	
			BEFORE QUINIDINE	AFTER QUINIDINE		BEFORE C. S. B.	AFTER C. S. B.		BEFORE C. S. B.	AFTER C. S. B.
1	10.0	46.0	140	40	5	40	60	in 7′ 15″	18	19
2	11.4	17.5	102	35	10	35	24	in 3′	18	24
							40	in 32″		
3	18.1	45.0	92	22	5	22	14	in 4′	20	21
							32	in 35′		
4	12.0	8.6	138	110	5	110	128	in 4′	23	46
5	12.0	45.0	128	70	5	70	45		42	44
							54	in 15′		
6	30.4	33.0	92	25	5	25	12	in 45″	20	23
							30	in 42′		
7	18.6	21.0	146	68	5	68	72	in 3′	20	32
							82	in 10′		

C. S. B., Caffeine sodium benzoate.

Table IV shows the results of experiments on seven dogs. Six of these dogs received 5 mg. of caffeine sodium benzoate per kilogram, and one received 10 mg. per kilogram. The experiments showed that this drug was a very good respiratory stimulant and a slight cardiovascular stimulant when dogs had received only small doses of quinidine. However, as the dose of quinidine reached the sublethal and lethal quantity, which is 45 mg. or more per kilogram, caffeine proved to have only a slight beneficial effect on respiration. It acted better, however, than coramine and picrotoxin.

Summary of Group I Drugs

The drugs in this group as a whole had little beneficial effect as circulatory stimulants. They proved, however, to have some value as respiratory stimulants, especially after small doses of quinidine had been given. The order of effectiveness was as follows: metrazol, caffeine sodium benzoate, coramine, picrotoxin.

GROUP II

This group includes paredrinol, benzedrine, paredrine, epinephrine, ephedrine, and neosynephrin.

The characteristic action of this group of closely related chemical compounds (Fig. 3) is to increase the blood pressure. All of them are sympathomimetic drugs whose characteristic pharmacologic effects are similar to those produced by stimulation of the sympathetic nervous system. In order to discover what effect and relative value this group of drugs has as analeptics in marked cardiovascular and respiratory depression caused by toxic and sublethal doses of quinidine, we performed the following experiment.

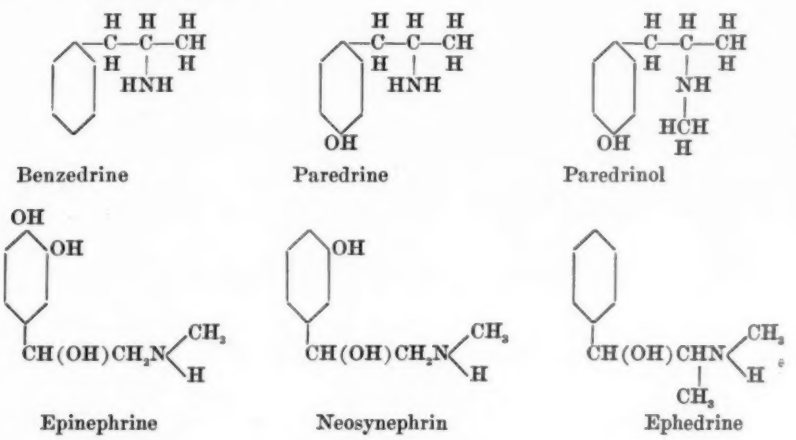


Fig. 3.

Dogs were anesthetized with pentothal sodium as in the previous experiments. Quinidine was given intravenously in small and in large doses. Tables V through X give the results of these studies.

After small doses of quinidine had been given, there was a marked rise in blood pressure after the administration of all these drugs. The rise in blood pressure was not so marked when the dose had been large. The exceptions were neosynephrin and epinephrine. Occasionally the blood pressure rise was greater after the administration of these drugs in the animals that had previously received large doses of quinidine. Tainter and Stockton[18] found that after they had cocainized cats by their method, the response to a given dose of epinephrine was increased from 32 per cent in the control to 59 per cent.

The degree of rise in blood pressure, the time required for the blood pressure to reach its maximum, and the length of time the blood pressure remained elevated varied with each of these drugs.

Paredrinol

Paredrinol is the American trade name for racemic parahydroxy-alpha-*N*-dimethyl-phenethylamine, marketed in Europe under the name "Veritol." It is an isomer of ephedrine. Much has been written in the foreign literature on experimental and clinical studies of this drug. Colombi,[19] in summing up the European literature on the beneficial effects of this compound on the circulation, states that they result from the following: (1) increased tone of the myocardium, (2) general arterial constriction, and (3) splanchnic constriction.

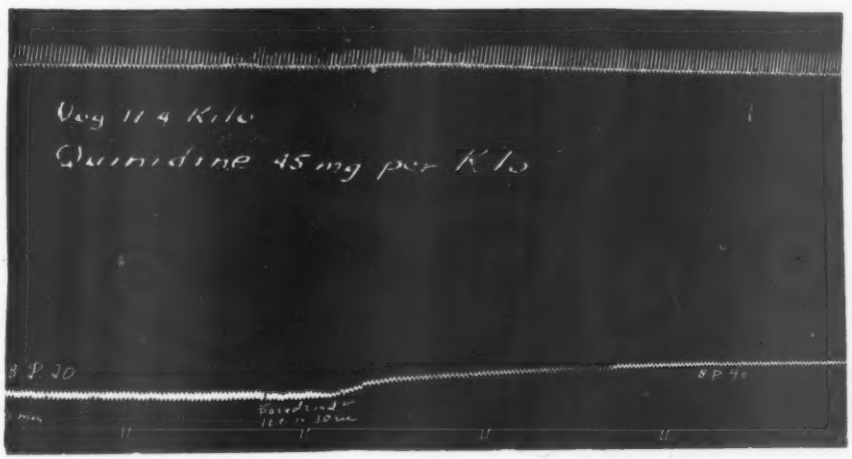


Fig. 4.—Effect of paredrinol after sublethal dose of quinidine.

In our experiments we found paredrinol fairly effective after small and large doses of quinidine had previously been given (Table V). The degree of blood pressure rise in response to paredrinol was less pronounced than in the case of paredrine. Paredrinol was, however, more effective than ephedrine (Fig. 4). The average blood pressure response after small and large doses had previously been given was very similar to

TABLE V

PAREDRINOL

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)	BLOOD PRESSURE		DOSE OF PAREDRINOL (MG. PER KG.)	BLOOD PRESSURE			RESPIRATION	
			BEFORE QUINIDINE	AFTER QUINIDINE		BEFORE PAREDRINOL	AFTER PAREDRINOL		BEFORE PAREDRINOL	AFTER PAREDRINOL
1	16.8	23.0	120	40	1.0	40	79	in 8′ 20″	20	29
2	10.0	46.0	140	80	10 Total	80	90	in 7′ 30″	25	24
3	17.5	23.0	140	74	10 Total	74	114	in 5′ 30″		N.C.
4	14.1	28.3	114	50	0.42		Died within 1′			
5	9.7	10.3	120	78	1.9	78	160	in 3′	18	16
6	10.5	45.0	155	88	1.0	88	94	in 6′	8	7
7	10.5	45.0	128	55	1.0	70	90	in 22′	15	17
8	17.7	45.0	134	72	0.3	98	26	in 3′ 30″	14	16
9	7.1	28.2	190	10	10 Total		Died within 1′			
10	12.7	8.6	155	128	1.0	128	154	in 3′ 30″	24	26
11	12.7	45.0	138	60	1.0	60	80	in 3′		N.C.

N.C., No change.

TABLE VI

BENZEDRINE

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)	BLOOD PRESSURE		DOSE OF BENZEDRINE (MG. PER KG.)	BLOOD PRESSURE			RESPIRATION	
			BEFORE QUINIDINE	AFTER QUINIDINE		BEFORE BENZEDRINE	AFTER BENZEDRINE		BEFORE BENZEDRINE	AFTER BENZEDRINE
1	9.7	20.0	112	86	1.0	86	128	in 1′ 30″	20	18
2	18.6	37.0	140	70	1.0	70	76	in 1′	23	24
3	10.45	57.0	138	50	0.94	50	70	in 30″	18	24
4	18.6	10.7	160	128	0.55	128	168	in 5′ 30″	13	15
5	10.45	9.6	134	112	0.5	112	144	in 6′ 30″	20	32
6	10.45	45.0	140	68	1.0	68	88	in 1′		N.C.
7	10.0	46.0	140	80	1.0	80	108	in 3′ 30″	21	20
8	16.8	23.8	156	80	1.0	80	118	in 1′ 30″	21	20
9	20.0	8.6	120	96	0.5	90	150	in 2′		N.C.
10	20.0	45.0	110	64	1.0	70	80	in 1′ 30″		N.C.
11	9.7	30.0	116	60	1.0	65	74	in 1′ 30″	–	–

N.C., No change.

that obtained with benzedrine. However, the benzedrine reaction time was definitely much faster, particularly after the large doses of quinidine. The duration of the paredrinol effect was about the same as that of paredrine.

Benzedrine

(phenylisopropylamine, amphetamine sulfate)

The pressor effect of this sympathomimetic amine was reported by Alles,[20] Hartung and Munch,[21] Tainter,[22] and many others. Alles,[20] in comparing the pressor effects of this drug with those of paredrine and epinephrine in dogs under barbital anesthesia, found benzedrine about $\frac{1}{100}$ to $\frac{1}{200}$ as effective as epinephrine (but its effects lasted longer than those of epinephrine) and about one-half as effective as paredrine.

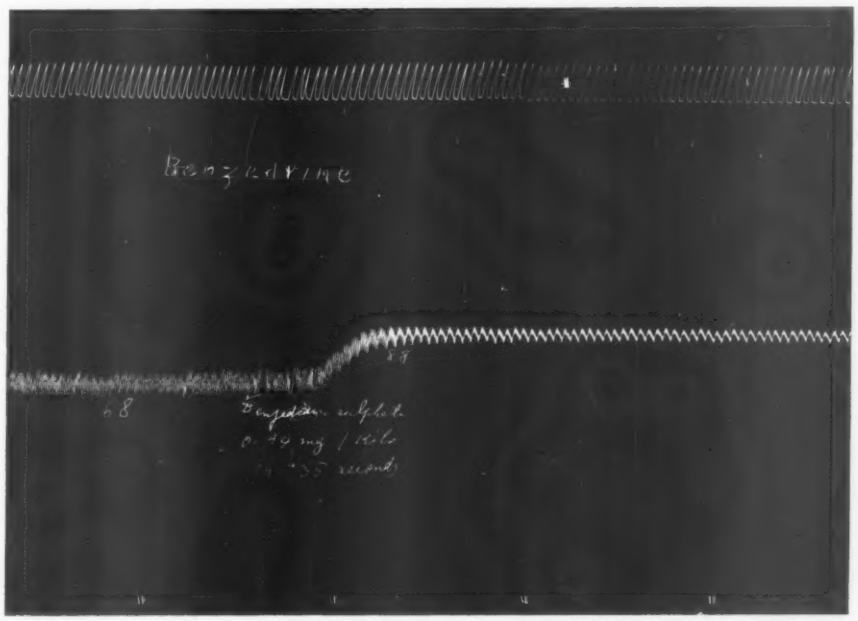


Fig. 5.—Effect of benzedrine after sublethal dose of quinidine. Dog weight, 10.45 kg. Dose of quinidine, 45 mg. per kilogram.

In our studies, we found, as is shown in Table VI, that benzedrine had definitely less pressor effect than paredrine and epinephrine, particularly when given to dogs that previously had received large doses of quinidine. Benzedrine was definitely more effective than ephedrine. The pressor effects of benzedrine and of paredrinol were very much alike, except for the time before the maximum pressor effect was reached after the administration of these drugs (Fig. 5). The maximum pressor effect of benzedrine was reached much more rapidly than that of paredrinol, paredrine, and ephedrine in dogs that previously had been given large doses of quinidine. The benzedrine action produced an

almost epinephrine-like response. The maximum rise in blood pressure was reached in about one and one-half minutes, compared with over eight minutes with paredrinol, three minutes with paredrine, and four minutes with ephedrine.

Paredrine

Alles[20] showed that paredrine had about twice the pressor effect of benzedrine in dogs under the effects of barbital anesthesia. Lohman, Rinkel and Myerson[23] found paredrine more effective than benzedrine in raising the blood pressure of patients. Nathanson[24] reported a study on the comparative action of paredrine, ephedrine, and epinephrine on cardiac standstill induced by pressure on the carotid sinus. He found paredrine at least twice as effective as ephedrine. He also found that paredrine, although its action was less intense than that of epinephrine, was superior because of its prolonged effect.

In our studies, paredrine was definitely more effective than paredrinol and benzedrine. The rise in blood pressure with paredrine was twice that of the rise with the other two drugs after the dog was under the effect of large doses of quinidine (Table VII, Fig. 6). The group as a whole caused a slowing of the pulse rate. Respiration was not affected by paredrine. The effect of paredrine on the blood pressure lasted about an hour.

Ephedrine

The average rise in blood pressure after giving ephedrine to dogs that had previously received small doses of quinidine was 24.4 mm. This is less than one-half the blood pressure rise obtained by giving paredrine under similar conditions. Abbott and Henry[25] found that ephedrine was about half as potent as paredrine when given orally.

The average rise in blood pressure after giving ephedrine to dogs that had previously received large doses of quinidine was about 15 mm. Four of the ten dogs in this series died shortly after the administration of ephedrine. It seems that ephedrine was of little analeptic value after sublethal doses of quinidine, especially when the blood pressure fell after large doses of quinidine to about 28 mm. or less. The average rise in blood pressure caused by ephedrine in this group was about half the blood pressure rise from paredrine after sublethal doses of quinidine had been given. Of the drugs in this group, ephedrine caused the least rise in blood pressure (Fig. 7).

Epinephrine

Table IX gives the results of our study with epinephrine. There was a definite rise in blood pressure after this drug was given to dogs that previously had received small and sublethal doses of quinidine. The doses of epinephrine were from 0.001 c.c. per kilogram (the amount

TABLE VII

PAREDRINE

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)	BLOOD PRESSURE		DOSE OF PAREDRINE (MG. PER KG.)	BLOOD PRESSURE			RESPIRATION	
			BEFORE QUINIDINE	AFTER QUINIDINE		BEFORE PAREDRINE	AFTER PAREDRINE		BEFORE PAREDRINE	AFTER PAREDRINE
1	12.3	8.0	140	120	0.8	130	190	in 3′ 35″	11	116
							139	in 17′		
2	12.3	48.8	139	56	0.8	56	72	in 7′		N.C.
3	21.0	45.0	120	36	0.5	36	70	in 1′	31	19
							90	in 17′		
4	21.0	8.6	120	100	0.1	100	170	in 3′	7	6
5	12.3	8.1	134	92	10.0	92	144	in 2′ 45″	10	10
6	12.3	40.5	130	30	10.0	30	78	in 2′ 55″	36	39
7	18.6	38.0	150	98	10.0	98	118	in 2′	-	-

N.C., No change.

TABLE VIII

EPHEDRINE

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)	BLOOD PRESSURE		PULSE		RESPIRATION		DOSE OF EPHEDRINE (MG. PER KG.)	BLOOD PRESSURE		PULSE		RESPIRATION	
			BEFORE QUINIDINE	AFTER QUINIDINE	BEFORE QUINIDINE	AFTER QUINIDINE	BEFORE QUINIDINE	AFTER QUINIDINE		BEFORE EPHEDRINE	AFTER EPHEDRINE	BEFORE EPHEDRINE	AFTER EPHEDRINE	BEFORE EPHEDRINE	AFTER EPHEDRINE
1	9.0	10	100	90 in 6′	182	156	27	22	1.0	90	132 in 1′	156	174	22	21
											108 in 6′		232		36
											104 in 24″		182		36
											106 in 40″		150		30
1	9.0	45	106	68 in 3′	150	150	30	30	2.5	68	78 in 1′	150	252	30	34
									5.5*	76	98 in 3′		208		31
											80 in 15′		246		48
											86 in 35′		240		84
2	14.5	10	130	100	176	138	19	12	1.0	100	120 in 30″	138	118	12	12
											No change in 15′		244		19
									1.0		N.C. in 30″		180		19
											172 in 30″		234		18
											124 in 15′		302		28
											126 in 30″		192		21
2	14.5	45	126	74	192	192	21	24	2.5	74	88 in 50″	192	174	24	25
											78 in 15′		260		30
											80 in 30″		200		23
3	15.8	10	100	82 end of inj.	140	126	17	15	0.25	82	100 in 1′	126	122	15	13
									0.25*	102	110 in 5′		142		12
									1.0*	110	120 in 55″		282		31
											114 in 5′		252		34
											110 in 15′		184		36
											110 in 30′		186		39
3	15.8	45	110	52 end of inj.	180	166	39	24	0.25	52	58	160	168	24	24
											60 5′		182		23
											66 15′		212		24
											68 1 hr.4′		136		150

*Five minutes later.

4	9.0	10	140	148 in 14″	172	110	11	8	0.25	148	168 in 1′ 134 in 5′ 130 in 15′ 130 in 30′	110	148 182 152 156	8	12 14 12 14
4	9.0	45	130	60	150	92	14	70	2.0	60	88 in 2′ 68 in 5′ 74 in 15′ 82 in 30′	92	158 130 150 136	10	10 9 10 11
5	7.8	10	116	70	200	132	17	11	1.0	70	114 in 1′ 120 in 5′ 106 in 14′ 98 in 30′ 100—1 hr. 50′	132	214 176 182 176 250	11	19 20 17 19 41
6	11.6	10	94	88	224	170	35	23	1.0	88	114 in 1′ 108 in 5′ 92 in 10′ 94 in 15′ 98 in 30′ 100 in 1 hr.	170	202 204 240 226 264 280	23	19 24 29 32 34 36
6	11.6	45	100	60 in 5′	280	192	36	22	5.0	60	72 in 5′ 68 in 10′ 66 in 15′ N.C. in 30′ 72 in 1 hr.	192	210 224 232 230 228	22	23 26 28 26 28
7	11.8	10	98	32					0.2 0.4 0.8 1.0 2.0 3.0 4.0	32 36 82 80 84 80 84	38 in 2′ 50 in 1′ 80 84 90 90 98				
7	11.8	45	84	22					1.0 2, 3, 4, 5, 8 8.0 8.0	22 30 32 20	30 32 26 6				
									Artificial respiration: died						

N.C., No change.

TABLE VIII—CONT'D

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)	BLOOD PRESSURE		PULSE		RESPIRATION		DOSE OF EPHEDRINE (MG. PER KG.)	BLOOD PRESSURE		PULSE		RESPIRATION	
			BEFORE QUINIDINE	AFTER QUINIDINE	BEFORE QUINIDINE	AFTER QUINIDINE	BEFORE QUINIDINE	AFTER QUINIDINE		BEFORE EPHEDRINE	AFTER EPHEDRINE	BEFORE EPHEDRINE	AFTER EPHEDRINE	BEFORE EPHEDRINE	AFTER EPHEDRINE
8	7.0	10	144	90					0.2	94	128 in 5′				
									0.4	124	134				
									0.8	132	150				
									1.0	131	154				
									2.0	132	172				
8	7.0	45	123	22					0.4						
									0.8						
									1.0						
									2.0						
									3.0						
									Artificial respiration: died						
9	9.5	10	142	76					0.2	76	80 in 1′45″				
									0.2	90	90				
									0.4	90	100 in 2″				
									0.8	94	104				
									1.0	84	92				
									2.0	88	108				
									3.0	90	108				
									4.0	98	122				
9	9.5	45	104	28					0.4						
									2.0						
									4.0						
									Artificial respiration: died						
10	7.0	10	142	88					0.2	88	112 in 1′				
									0.3	112	122				
									0.4	122	146				
									0.5	146	136				
									0.6	134	148				
									0.7	148	150				
									0.8	132	158				
									0.9	158	160				
									1.0	N.C.					
									2.0	N.C.					
									2.5	160	170				

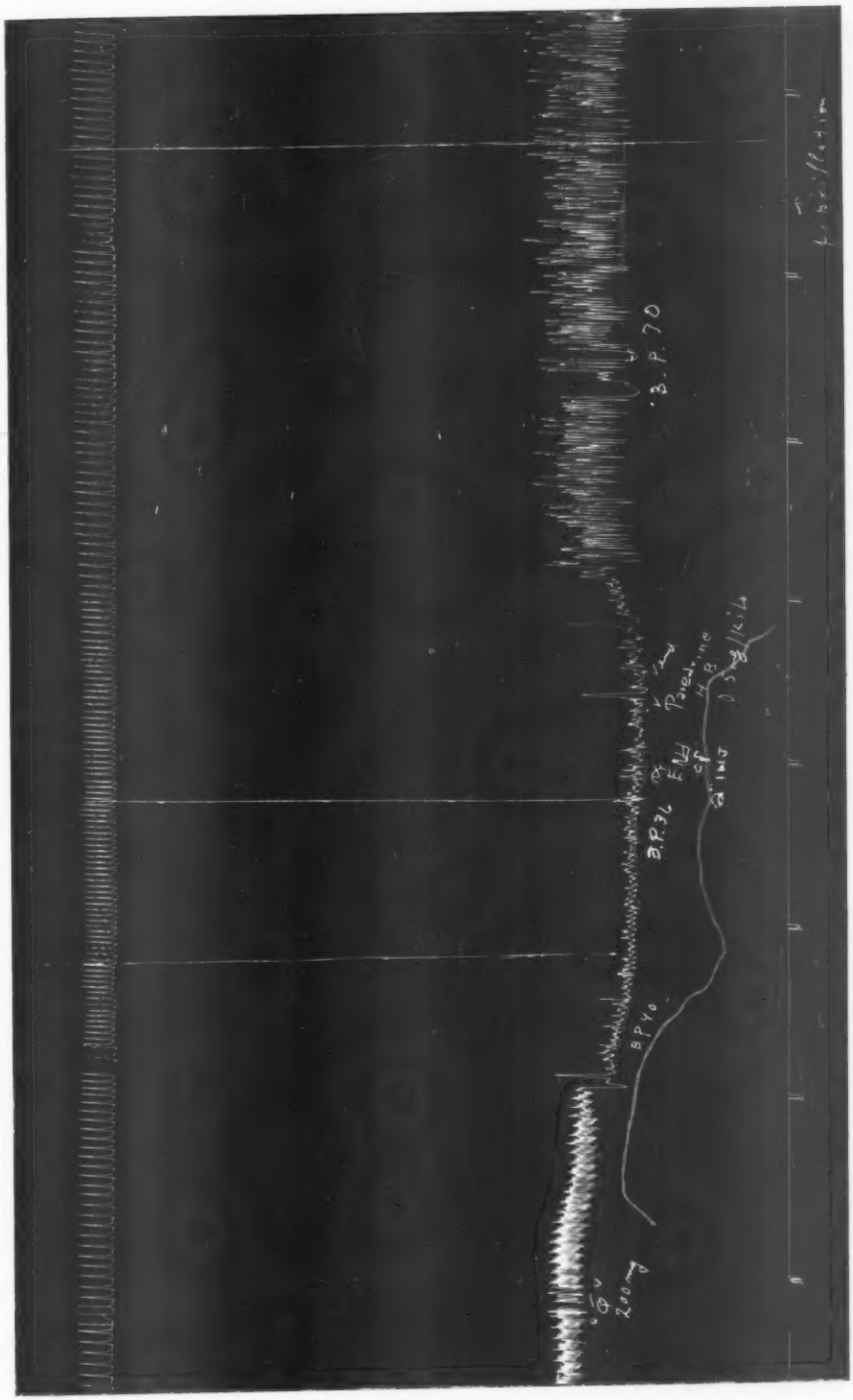


Fig. 6.—Effect of paredrine after sublethal dose of quinidine. Dog weight, 21.0 kg. Dose of quinidine, 45 mg. per kilogram.

TABLE IX

EPINEPHRINE

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)	BLOOD PRESSURE		PULSE		RESPIRATION		DOSE OF EPINEPHRINE (C.C. PER KG.)	BLOOD PRESSURE		PULSE		RESPIRATION	
			BEFORE QUINIDINE	AFTER QUINIDINE	BEFORE QUINIDINE	AFTER QUINIDINE	BEFORE QUINIDINE	AFTER QUINIDINE		BEFORE EPINEPHRINE	AFTER EPINEPHRINE	BEFORE EPINEPHRINE	AFTER EPINEPHRINE	BEFORE EPINEPHRINE	AFTER EPINEPHRINE
1	17.0	10	106	92 in 3′	117	112	21	18	0.005	92	130 in 1′ 92 in 15′ 92 in 30″ 110 in 1 hr.	112	122 112 108 114	18	18 20 23 21
1	17.0	45	110	62 end of inj.	80	100	21	24	0.005	62	72 in 30″ 76 in 10′ 78 in 15′ 80 in 30′	100	137 114 106 124	24	23 23 27 24
2	14.6	10	155	100 in 4′	166	136	27	27	0.005	100	132 in 30″ 110 in 15′ 110 in 30′ 114 in 1 hr.	136	138 162 150 150	27	31 27 26 38
2	14.6	45	120	46 in 4′	178	184	30	31	0.06	46	120 in 45″ 46 in 5′ 64 in 15′ 70 in 30′ 70 in 1 hr.	124	168 138 132 150 150	31	28 36 28 28 28
3	9.3	10	140	124 in 3′	180	166	19	13	0.005	124	154 in 55″ 138 in 5′ 134 in 15′ 122 in 30′	166	140 132 128 168	13	17 11 10 15
3	9.3	45	146	38 end of inj.	170	60	13	15	0.06	38	128 in 1′ 50 in 5′ 58 in 15′	60	200 105 90	15	18 19 20

1 c.c. = 48.75 mg.

4	12.5	10	78	60					(0.001)	60	80 in 30″					
									0.001	68	114 in 1′					
									0.002	70	118 in 45″					
									0.003	68	132 in 1′					
									0.004	68	142 in 1′ 15″					
									0.005	68	142 in 1′ 30″					
									0.006	68	132 in 1′					
4		20	78	60					0.001	60	65 in 10″					
									0.001	58	66 in 15″					
									0.002	54	60 in 10″					
									0.003	56	68 in 15″					
									0.004	56	70 in 30″					
									0.005	60	90 in 30″					
									0.006	62	98 in 1′					
									0.007	62	104 in 1′					
5	11.8	10	118	60					Neosyn.							
									0.001	60	75 in 15″					
									0.002	70	108 in 35″					
									0.003	64	118 in 40″					
									0.004	82	132 in 55″					
									0.005	90	148 in 1′					
									0.006	120	162 in 1′					
5		20	120	45					0.001	45	56 in 30″					
									0.002	68	72 in 30″					
									0.003	72	76 in 40″					
									0.004	72	88 in 30″					
									0.005	74	89 in 35″					
									0.006	74	92 in 35″					
									0.01	76	100 in 1′					
									0.02	82	108 in 1′					

TABLE IX—CONT'D

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)	BLOOD PRESSURE		PULSE		RESPIRATION		DOSE OF EPINEPHRINE (C.C. PER KG.)	BLOOD PRESSURE		PULSE		RESPIRATION	
			BEFORE QUINIDINE	AFTER QUINIDINE	BEFORE QUINIDINE	AFTER QUINIDINE	BEFORE QUINIDINE	AFTER QUINIDINE		BEFORE EPINEPHRINE	AFTER EPINEPHRINE	BEFORE EPINEPHRINE	AFTER EPINEPHRINE	BEFORE EPINEPHRINE	AFTER EPINEPHRINE
6	8.6	10	128	100					0.001	100	152 in 1′				
									0.002	132	162 in 1′				
									0.003	120	170 in 40″				
									0.004	110	182 in 1′				
									0.005	110	210 in 1′				
6	8.6	45	116	30					0.001	30	40 in 20″				
									0.002	36	80 in 45″				
									0.003	36	84 in 1′				
									0.004	48	116 in 1′				
									0.005	80	130 in 45″				
									0.006	70	144 in 1′				
6	8.6	27	68	35					0.03	35	96 in 1′				
									0.002	38	52 in 20″				
									0.003	36	86 in 45″				
									0.004	44	106 in 1′				
									0.005	46	118 in 1′				
8	11.8	10	106	90					0.001	90	112 in 1′				
									0.002	106	114 in 55″				
									0.003	112	134 in 55″				
									0.004	110	120 in 1′				
									0.005	110	148 in 45″				
									0.006	108	152 in 55″				

8	11.8	45	90	40					0.001	40	48 in 5″				
									0.002						
									0.002	30	54 in 5″				
									0.002						
									0.003	30	38 in 5″				
									0.003	40	42 in 5″				
									0.004	40	52 in 15″				
									0.005	48	50 in 20″				
									0.006	40	52 in 45″				
									0.007	48	66 in 45″				
									0.008	58	60 in 1′				
									0.009	60	68 in 5″				
									0.01	66	94 in 45″				
									0.02	40	82 in 1′				
9	6.8	10	126	90					0.001	119	172 in 1′				
9	6.8	45	120	30					0.001	30	40 in 15″				
									0.002	35	64 in 55″				
									0.003	48	98 in 45″				
									0.004	66	80 in 1′				
									0.005	72	80 in 30″				
									0.006	76	112 in 1′				
									0.007	80	130 in 1′				
									0.008	84	120 in 55″				
									0.009	94	134 in 40″				
									0.01	92	182 in 1′				

Note: Time interval between doses was 5 to 10 minutes.

TABLE X

NEOSYNEPHRIN

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)	BLOOD PRESSURE		PULSE		RESPIRATION		DOSE OF NEOSYNEPHRIN (C.C. PER KG.)	BLOOD PRESSURE		PULSE		RESPIRATION	
			BEFORE QUINIDINE	AFTER QUINIDINE	BEFORE QUINIDINE	AFTER QUINIDINE	BEFORE QUINIDINE	AFTER QUINIDINE		BEFORE NEOSYNEPHRIN	AFTER NEOSYNEPHRIN	BEFORE NEOSYNEPHRIN	AFTER NEOSYNEPHRIN	BEFORE NEOSYNEPHRIN	AFTER NEOSYNEPHRIN
1	17.0	10	98	82 in 5′	160	20	17	13	0.005	82	160 in 1′	120	94	13	10
											100 in 5′		95		15
											98 in 15′		130		16
											96 in 30′		130		14
											98 in 1 hr.		130		16
1	17.0	45	102	62 in 5′	157	116	16	20	0.06	62	162 in 1′ 30″	116	220	20	32
											111 in 5′		138		38
											92 in 10′		144		27
											80 in 15′		140		26
											78 in 30″		135		25
											80 in 1 hr.		124		21
2	11.0	10	120	100 in 5′	182	132	14	12	0.005	100	160 in 1′	132	152	12	18
											147 in 5′		142		17
											100 in 25′		120		12
											108 in 1 hr. 7′		152		15
											112 in 1 hr. 10′		164		18
2	11.0	45	112	30 in 12′	164	88	18	14	0.06	30	140 in 1′	88	168	14	23
											122 in 5′		182		21
											90 in 15′		118		20
											90 in 30′		160		20
											98 in 1 hr.		126		20
3	9.0	10	124	118 in 5′	188	128	10	11	0.005	118	218 in 1′	128	116	11	16
											170 in 5′		160		26
											120 in 15′		198		17
											110 in 30″		152		18
											116 in 45′		182		18

3	9.0	45	116	68 in 5′	182	118	18	18	0.06	68	178 in 1′ 102 in 5′ 76 in 15′ 76 in 30′ 70 in 1 hr. 15′	118	184 198 204 160 136	18	24 34 36 44 90
4	14.3	10	92	100 in 5′	150	100	9	9	0.005	100	210 in 1′ 150 in 5′ 100 in 35′ 108 in 1 hr.	100	98 106 128 106	9	15 15 12 12
4	14.3	45	118	112 in 5′	106	174	14	22	0.03	112	230 in 35′ 142 in 5′ 162 in 10′ 116 in 20′ 122 in 30′ 114 in 1 hr.	174	188 159 134 130 164 160	22	23 22 20 21 20 24
5	11.25	10	92	88 in 5′	200	122	28	18	0.005	88	180 in 1′ 90 in 15′ 110 in 30′ 112 in 1 hr.	122	98 186 206 156	18	16 29 32 24
6	8.7	10	120	90					0.001 0.002 0.003	90 98 102	108 in 40″ 160 in 55″ 200 in 1′				
6		45	128	220					0.001 0.002 0.003 0.004 0.005 0.006	20 26 52 68 80 90	28 in 20″ 48 in 35″ 94 in 45″ 130 in 45″ 156 in 1′ 170 in 1′ 10″				
7		10	86	40					0.001 0.002 0.003	40 50 58	70 in 40″ 104 in 55″ 140 in 1′ 10″				

TABLE X—CONT'D

DOG	WEIGHT (KG.)	DOSE OF QUINIDINE (MG. PER KG.)	BLOOD PRESSURE		PULSE		RESPIRATION		DOSE OF NEOSYNEPHRIN (C.C. PER KG.)	BLOOD PRESSURE		PULSE		RESPIRATION	
			BEFORE QUINIDINE	AFTER QUINIDINE	BEFORE QUINIDINE	AFTER QUINIDINE	BEFORE QUINIDINE	AFTER QUINIDINE		BEFORE NEOSYNEPHRIN	AFTER NEOSYNEPHRIN	BEFORE NEOSYNEPHRIN	AFTER NEOSYNEPHRIN	BEFORE NEOSYNEPHRIN	AFTER NEOSYNEPHRIN
7		45	82	28					0.001	28	34 in 15″				
									0.002	30	40 in 15″				
									0.003	34	50 in 20″				
									0.004	44	62 in 30″				
									0.005	50	78 in 35″				
									0.006	60	80 in 30″				
									0.007	64	104 in 55″				
									0.008	74	124 in 55″				
									0.009	86	142 in 1′				
									0.01	92	152 in 1′				
									0.02	90	158 in 1′				
									0.03	98	164 in 1′				
8	10.0	10	140	65					0.001	65	108 in 1′ 10″				
									0.002	86	174 in 1′ 30″				
8	10.0	45	120	20					0.001 0.002 0.002	20	64 in 1′ 55″				
									0.003	50	72 in 35″				
									0.004	58	86 in 35″				
									0.005	62	98 in 40″				
									0.006	74	118 in 55″				
									0.007	82	138 in 55″				
									0.008	90	150 in 1′				
									0.009	96	158 in 1′				
									0.01	102	164 in 55″				

Note: Time interval between doses was ten to fifteen seconds.

used as a control) to 0.01 per kilogram. For comparing the analeptic value with that of the other drugs, we chose the experiments in which a dose of 0.005 per kilogram was used, or occasionally smaller amounts. In two of our earlier experiments—Dogs 2 and 3—in which sublethal doses of quinidine had been given, we gave large doses of ephedrine, i.e., 0.06 per kilogram.

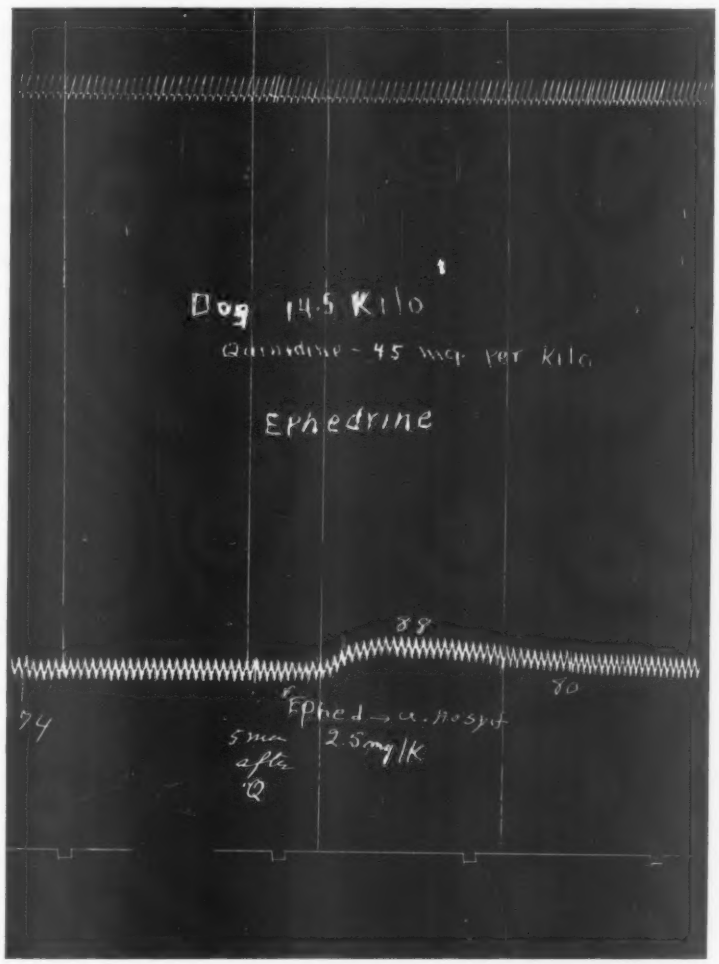
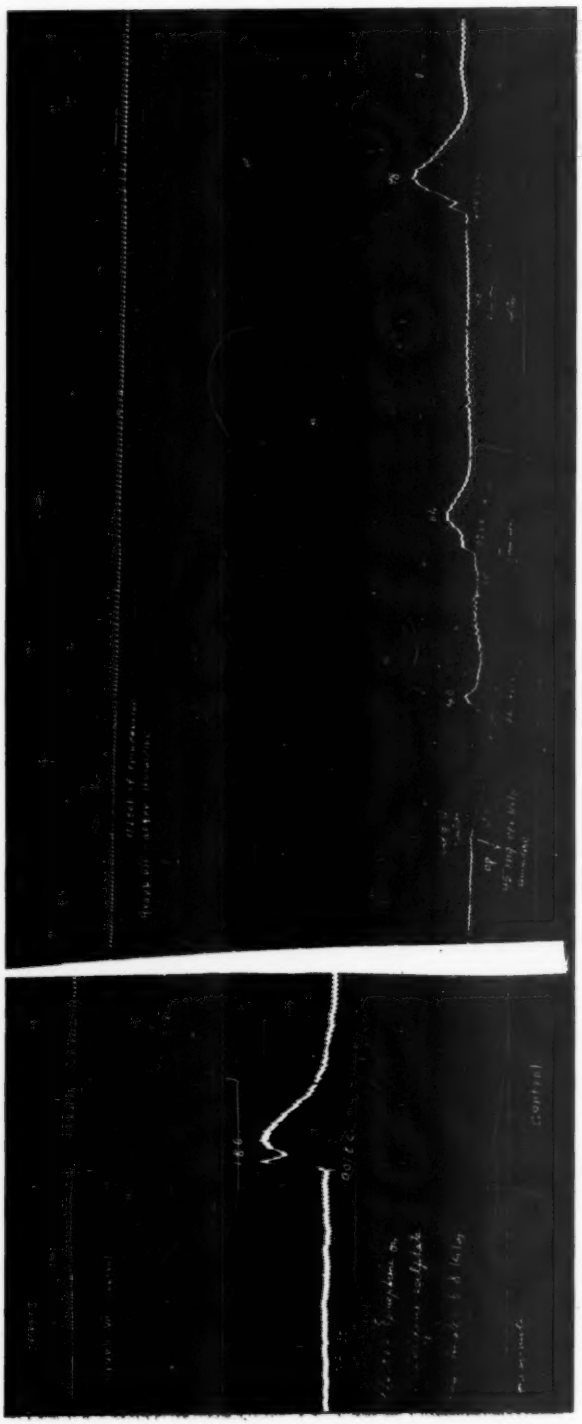


Fig. 7.—Effect of ephedrine after sublethal dose of quinidine.

The rise in blood pressure after epinephrine was, on the average, greater than in the case of any of the other drugs, with the exception of neosynephrin. However, when doses as small as 0.001 c.c. per kilogram were used, it appeared that epinephrine had a greater effect on the blood pressure than neosynephrin. The average rise in blood pressure after administering epinephrine to dogs that previously had received



A. *B.*

Fig. 8.—*A*, Control. *B*, After dog had been given 45 mg. of quinidine per kilogram.

small doses of quinidine was 46.8 mm. and 44.0 mm. in dogs that had been given sublethal doses of quinidine.

The maximum effect was fastest with epinephrine. The height of the blood pressure was reached, on the average, in fifty-three seconds in dogs that had previously received small doses of quinidine, and a little faster (forty-one seconds) in dogs that had received sublethal doses of quinidine (Table XI).

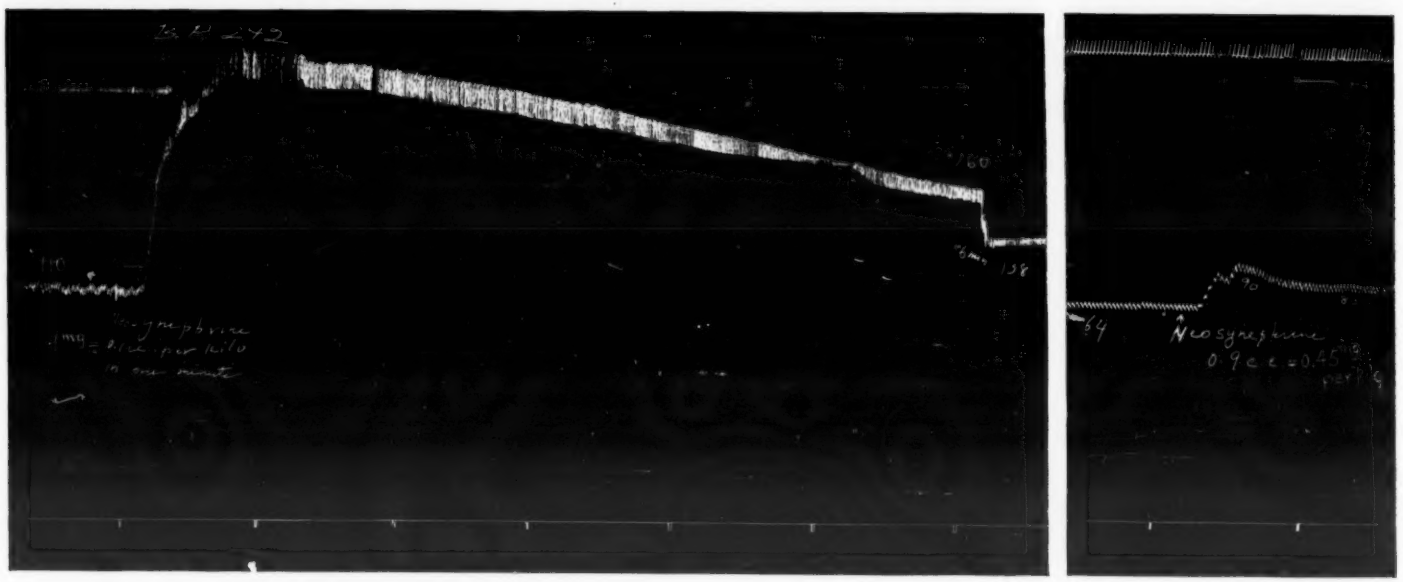
Neosynephrin

Neosynephrin hydrochloride is a levo-alpha-hydroxy-beta-methyl-amino-3-hydroxy-ethyl benzene hydrochloride. It is very closely related structurally to epinephrine.

The administration of this substance caused a greater rise in blood pressure than any of the others in this sympathomimetic group, both after the animals had previously been given small doses of quinidine and after they had received large doses (Table X). The next most effective drug was epinephrine, although epinephrine was about half as effective as neosynephrin when given to dogs that previously had received small or large doses of quinidine (Fig. 9).

Quinidine may affect the pressor response of these two drugs. Tainter and Stockton[18] injected ergotamine intravenously into cats, in an average dose of 0.7 mg. per kilogram, which was enough to paralyze the sympathetic vasoconstrictors. The average control (a 48 per cent rise in blood pressure after epinephrine) was reversed to a fall of 21 per cent. The average control rise of 55 per cent after levo-meta-synephrin was decreased to an average rise of 21 per cent, but was not reversed. Ajazzi and Graubner[26] report that in the isolated rabbit's heart the paralyzing effect of quinidine on the heart is completely suppressed by neosynephrin, and particularly by epinephrine. Quinidine has the same inhibiting action against neosynephrin which makes these drugs mutually antagonistic.

In a few experiments, in which larger doses of neosynephrin and epinephrine were used, the difference in response between these two drugs was not so pronounced; however, neosynephrin caused a definitely greater pressor response. The pressor effect of neosynephrin lasted about fifteen minutes, whereas the pressor effect of epinephrine lasted less than half that time. In this study we did not observe the consistent slowing of the heart rate reported by Johnson,[27] Keys and Violante[28, 29] Bittrich,[30] and Lorhan and Oliverio.[31] The maximum rise in blood pressure from neosynephrin in our experiments was reached, on the average, in fifty-eight seconds after small doses of quinidine had previously been given, and fifty-five seconds after sublethal doses of quinidine had previously been given. Epinephrine acted a little faster, i.e., fifty-three seconds after small doses of quinidine and forty-one seconds after sublethal doses of quinidine.



A. *B.*

Fig. 9.—Effect of neosynephrin after sublethal doses of quinidine. *A*, 1 mg. of neosynephrin per kilogram after 37.6 mg. of quinidine per kilogram. *B*, 0.45 mg. of neosynephrin per kilogram after 50 mg. of quinidine per kilogram.

CONCLUSIONS

1. Coramine, picrotoxin, metrazol, and caffeine sodium benzoate were of some value as respiratory stimulants when depression of the cardiovascular and respiratory systems had been induced by small doses of quinidine.

TABLE XI

	AV. RISE IN BLOOD PRESSURE AFTER				AV. TIME FOR MAXIMUM RISE OF BLOOD PRESSURE AFTER			
	SMALL DOSE QUINIDINE		LARGE DOSE QUINIDINE		SMALL DOSE QUINIDINE		LARGE DOSE QUINIDINE	
Benzedrine	40 mm.	42	17 mm.	20	3′48″	1′30″	1′30″	1′00″
	(av.)	40		20		5′30″		0′30″
		32		28		6′30″		1′00″
		54		20		2′00″		3′30″
		38		9		1′30″		1′30″
				6				1′30″
Paredrinol	42 mm.	39	16 mm.	10	5′5″	8′20″	8′48″	7′30″
	(av.)	40		6		5′30″		Died
		62		20		3′00″		6′00″
		26		26		3′30″		22′00″
				20				3′30″
								Died
								3′00″
Paredrine	64 mm.	70	29.5 mm.	16	3′17″	3′35″	3′18″	7′00″
	(av.)	70		34		3′30″		1′00″
		52		48		2′45″		2′55″
				20				2′00″
Ephedrine	25.8 mm.	42	14.5 mm.	10	1′54″	1′30″	4′20″	1′00″
	(av.)	20	(av.)	14	(av.)	0′30″	(av.)	0′50″
		18		14		1′00″		15′00″
		20		28		1′00″		2′00″
		50		12		5′00″		5′00″
		26		Died		1′00″		
		14		Died		1′00″		
		34		Died		5′00″		
		10		9		2′00″		2′00″
		24				1′00″		
Neosynephrin	88.5 mm.	78	84 mm.	100	58″	1′00″	55″	1′30″
	(av.)	60	(av.)	110	(av.)	0′45″	(av.)	1′00″
		100		118		1′00″		1′00″
		110		118		1′00″		0′35″
		92		76				1′00″
		98		28		0′60″		0′35″
		82		36		1′10″		1′10″
		88				0′30″		
Epinephrine	46.8 mm.	38	44 mm.	10	0′53″	1′00″	0′41″	0′30″
	(av.)	32	(av.)	74	(av.)	0′30″	(av.)	0′46″
		30		90		0′55″		1′00″
		100		8		0′60″		0′30″
		38		2		0′45″		0′20″
		74		50		1′30″		0′45″
		15		72		0′35″		1′00″
		58				1′00″		
		30				0′30″		
		53				0′60″		

2. The order of effectiveness of these drugs as respiratory stimulants in light quinidine depression was as follows: metrazol, caffeine sodium benzoate, coramine, picrotoxin.

3. After large doses of quinidine, depression was often aggravated by metrazol, coramine, and picrotoxin.

4. Paredrinol, ephedrine, benzedrine, paredrine, epinephrine, and neosynephrin showed definite value as circulatory stimulants, after both small and sublethal doses of quinidine (Table XI).

5. Ephedrine, epinephrine, and benzedrine also showed definite respiratory effects. There was some evidence that paredrinol produced respiratory stimulation, although very little.

6. Ephedrine was the least effective in counteracting the circulatory depression caused by small or large doses of quinidine.

7. The effect of benzedrine and paredrinol on the blood pressure rise was very much the same; however, the time of appearance of the maximum rise in blood pressure after the administration of these drugs was definitely much shorter after giving benzedrine.

8. The effect of neosynephrin lasted twice as long as that of epinephrine.

9. Paredrine was one of the most valuable pressor substances in this group. It was about twice as effective as ephedrine, benzedrine, or paredrinol. Although the blood pressure response was much less after its administration, compared to that to epinephrine and neosynephrin, the effect of paredrine lasted much longer.

10. The most effective pressor substance in this group was neosynephrin. The blood pressure response was about twice as high, and the effect lasted twice as long after giving neosynephrin as after administering epinephrine, after both small and large doses of quinidine.

I wish to express my sincere appreciation to Dr. A. D. Hirschfelder for his valuable suggestions and cooperation in carrying out the experiments described in this paper and, also, to Mr. G. Tamcales, for his technical assistance.

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Department of Clinical Reports

VENTRICULAR TACHYCARDIA STOPPED ON THE TWENTY-FIRST DAY BY GIVING QUINIDINE SULFATE INTRAVENOUSLY

Report of a Case

Alfred W. Dubbs, M.D., and David H. Parmet, M.D.
Allentown, Pa.

THE following report describes a case of ventricular tachycardia which occurred in a patient who was subject to attacks of bronchial asthma. The tachycardia followed the administration of epinephrine in oil, and continued without interruption for twenty-one days. Quinidine sulfate, administered intravenously,[1] caused immediate and dramatic cessation of the tachycardia.

CASE REPORT

S. B., a white man, aged 52, was admitted to the Sacred Heart Hospital complaining chiefly of a fluttering sensation in the epigastrium. This symptom had appeared suddenly two days previously and persisted without interruption. The patient had always enjoyed good health except for periodic attacks of bronchial asthma. These attacks, which had appeared irregularly for the preceding three years, always responded promptly to the administration of ephedrine by mouth.

On the evening prior to the onset of the above complaint, the patient was seized with an attack of asthma. The family physician was called, and, instead of prescribing the usual dose of ephedrine, epinephrine suspended in oil was administered parenterally. The asthma subsided; the patient fell asleep; and, the following morning, upon awakening, he noted a fluttering sensation in the epigastrium, accompanied by a feeling of nausea. His physician was again called, and the chief abnormality was a tachycardia with a rate of 180 beats per minute. Two days later, after there had been no response to sedation, vagal stimulation, and precordial ice cap, the patient was admitted to the hospital.

Physical examination upon admission revealed a white man who was lying comfortably in bed. A few scattered râles at the bases of the lungs and a tachycardia with a rate of 170 beats per minute were the only objective signs. The blood pressure was 90/58. Shortly after admission the patient complained of inability to void, and catheterization was done. It was necessary to continue this procedure throughout the course of the illness. The blood cell counts were normal. The urine was negative except for a slight trace of albumin. The blood Wassermann reaction was negative. The electrocardiogram (Fig. 1*A*) revealed a tachycardia which was interpreted as being ventricular in origin.

The patient was given 25 grains of quinidine sulfate by mouth daily, starting on the third day of the tachycardia, and this was continued for one week with no effect. On the tenth day of the disease the patient began to have symptoms of

From the Department of Electrocardiography, Sacred Heart Hospital.
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congestive failure. There were signs of fluid in the right pleural sac, and the edge of the liver extended below the costal margin and was definitely tender. The right side of the chest was tapped on four occasions between the twelfth and twenty-first day of the disease, and a total of 4,610 c.c. of transudate was removed.

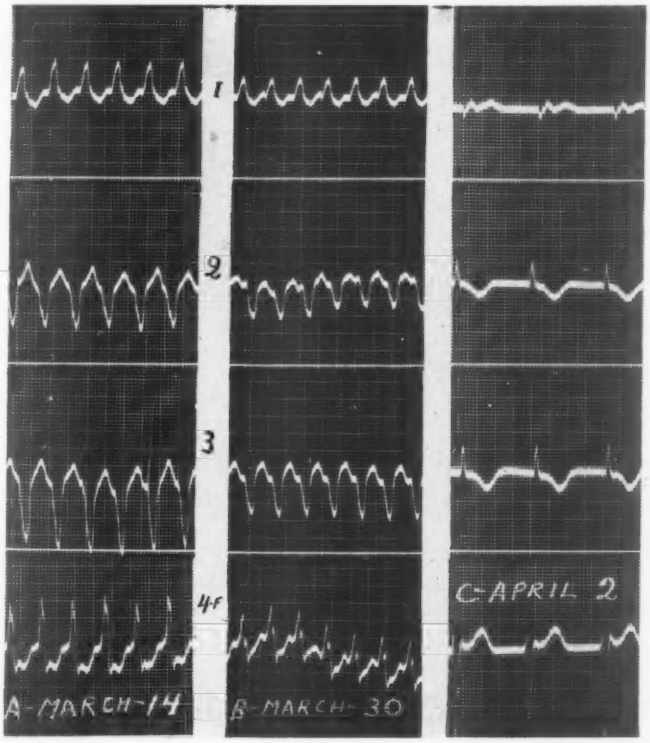

Fig. 1.—*A* and *B*, Electrocardiograms taken during the paroxysm of ventricular tachycardia. *C*, Electrocardiogram taken fifteen minutes after cessation of the tachycardia.

Digitalis was started on the tenth day, and a sufficient quantity was given to cause complete digitalization, but there was no effect on the heart rate or congestive signs and symptoms. Eserine sulfate was started at the same time, in 1.4 gr. doses three times a day, and stopped after a day's trial because of nausea and vomiting. On the twelfth day aminophyllin in 3½ gr. doses was given intravenously every four hours, and oxygen by nasal catheter was started. The former had no effect upon any of the patient's symptoms, and was discontinued. The oxygen was given throughout the remainder of the illness. On the fourteenth day 0.25 mg. of mecholyl was given subcutaneously. This was immediately followed by a generalized flush, sweating, a sense of tightness in the chest, and nausea and vomiting. We realized that mecholyl is used primarily to control the auricular type of tachycardia, but felt that a trial was warranted. It had no effect upon the cardiac rate in this case. On the seventeenth day quinine dihydrochloride (5 grains in 25 c.c. of normal saline) was administered intravenously with no change. On the eighteenth day 2 c.c. of a 50 per cent solution of magnesium sulfate were given intravenously with no effect. The electrocardiogram (Fig. 1*B*) on the nineteenth day of the tachycardia was essentially the same as the previous tracing.

The patient rapidily became weaker and a state of shock supervened. His mental attitude changed from one of cooperation to marked apathy and despondency.

Food was refused and death was welcomed. The signs of congestive failure increased. There were cyanosis, orthopnea, recurring effusion in the right pleural sac, coarse râles at the base of the left lung, and a tender liver edge 4 fingerbreadths below the costal margin. The abdomen was moderately distended, and the urinary retention persisted.

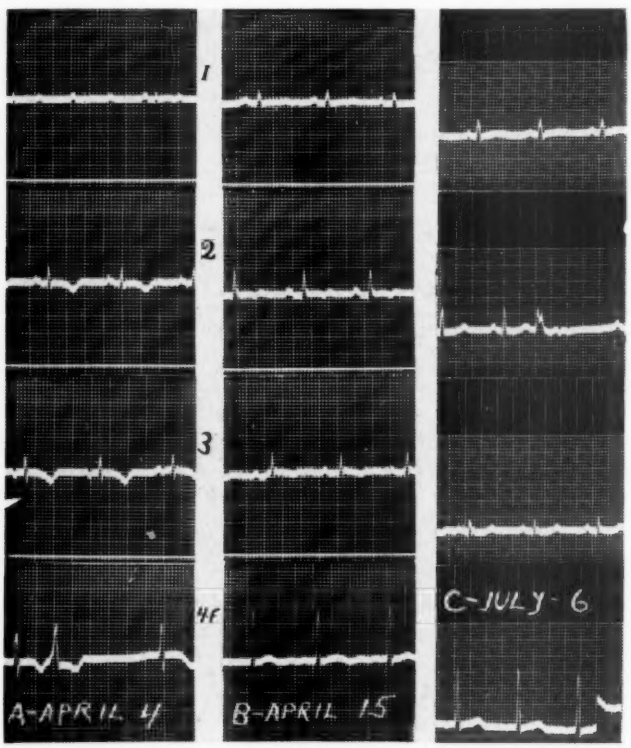

Fig. 2.—*A*, *B*, and *C*, Electrocardiograms taken after cessation of the tachycardia.

On the twenty-first day, when hope for the patient's recovery was practically exhausted, 15 grains of quinidine sulfate, dissolved in 90 c.c. of sterile distilled water, were administered intravenously. Prior to this the apex rate was 148 per minute and the blood pressure was 92/80. Half of the above solution had entered the vein when the rate suddenly fell to 68 per minute and the blood pressure rose to 106/74. The change in the patient was just as spectacular. He immediately became alert and expressed an interest in what was happening. His general state changed from one of extreme apathy to one of relative brightness. There was a moderate amount of nausea and vomiting immediately after the drug was given, but this rapidly subsided. His recovery from this point was continuous, uneventful, and apparently complete. An electrocardiogram (Fig. 1*C*) which was taken fifteen minutes after the rate change showed nodal rhythm and a ventricular rate of 80. The patient continued to take 5 grains of quinidine sulfate by mouth three times a day for one week after the cessation of the tachycardia.

DISCUSSION

The authors felt that reporting this case was justifiable if only to bring to the attention of the reader, not a new method[2-5] of treatment

for ventricular tachycardia, but one that they feel is too frequently referred to as a measure of last resort. In this case it was undoubtedly life saving, and, had it been used sooner, there is no reason to believe that the results would not have been the same.

Prior to the intravenous administration of quinidine sulfate the drug had been given in large doses by mouth with no effect. In addition, there was no response to numerous other preparations which have been suggested as means of controlling this form of tachycardia.

With the report we present a series of electrocardiograms (Figs. 1 and 2) which were taken during the course of the tachycardia and after it ceased. The tracing immediately after cessation of the tachycardia (Fig. 1*C*) is of particular interest because of the conduction and T-wave changes. The rhythm (Fig. 1*C*) after the disappearance of tachycardia was nodal. This rapidly changed to normal sinus rhythm (Fig. 2*A*). The T-wave changes in Leads II and III (Fig. 1*C*) apparently were not the result of a recent myocardial accident, for the change from marked inversion to a more normal form (Fig. 2*A*, *B*, and *C*) was quite rapid. In addition, the rapid clinical improvement after cessation of the tachycardia would seem to be additional evidence that this is so. The change in the rhythm and inversion of the T waves of this character very likely reflect extreme myocardial fatigue and exhaustion, resulting from the long-continued tachycardia. McMillan and Bellet[6] observed similar T-wave changes in the electrocardiogram of a 16-year-old girl after a paroxysm of ventricular tachycardia. They were of the opinion that the heart in their case was undamaged. The flattened T waves in Lead I (Fig. 2*A*, *B*, and *C*), together with an occasional ventricular extrasystole, suggest some myocardial abnormality in our case, and this may have been a factor in initiating the tachycardia.

CONCLUSION

A case of ventricular tachycardia which was stopped on the twenty-first day of the paroxysm by the administration of quinidine sulfate intravenously is reported.

Electrocardiograms taken during the tachycardia and afterward, showing interesting conduction and T-wave changes, are included.

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6. McMillan, Thomas, and Bellet, Samuel: Ventricular Paroxysmal Tachycardia; Report of a Case in a Pregnant Girl of Sixteen Years With an Apparently Normal Heart, AM. HEART J. **7**: 70, 1931.

Department of Reviews and Abstracts

Selected Abstracts

Caeiro, A.: Velocity of Propagation of the Different Waves of the Venous Pulse. Rev. argent. de cardiol. **8**: 329, 1941.

Velocity of propagation of the different waves of the venous pulse were measured in the dog with an efficient method. In general their propagation is much slower than those of the arterial pulse. The averages vary between 0.85 and 4.69 per second, the different accidents of the venous pulse having different velocities of propagation.

The beginning of the v wave, being a stagnation phenomenon, propagates very slowly (0.85 m. per second). The apex of the v wave which is purely a pressure variation propagates much more rapidly (3.86 m. per second). The beginning apex and end of a and the end of v which represent a mixture of pressure and volume variations have a medium velocity of propagation (1.39, 1.4, and 1.24 m. per second, respectively). Of the accidents of the venous pulse which are not properly of venous origin, the second sound is the more rapidly propagated due to its proper physical characteristic (4.69 m. per second). The c wave has a velocity of propagation which statistically can be considered as equal to that of the mixed waves already mentioned (1.68 m. per second).

AUTHOR.

Hahn, P.: Does the Heart Work as a Pressure Pump or as a Hydraulic Ram? Cardiologia **5**: 308, 1941.

The author discusses Havlíček's theory comparing the heart to a hydraulic ram and gives his reasons for being unable to accept that theory.

AUTHOR.

Sigler, L. H.: The Hyperactive Cardioinhibitory Carotid-Sinus Reflex as an Aid in the Diagnosis of Coronary Disease. Its Value Compared With That of the Electrocardiogram. New England J. Med. **226**: 46, 1942.

A comparative study is presented of the incidence of a hyperactive cardioinhibitory carotid-sinus reflex and of electrocardiographic abnormalities in a series of 1,073 cases, mostly ambulatory, of coronary disease. It was found that 91.3 per cent of the males and 72.6 of the females in this series showed the cardioinhibitory response, whereas only 63 per cent of the males and 71.9 of the females showed abnormalities in the electrocardiogram. High degrees of cardioinhibitory response, which are definitely abnormal, occurred in 61.8 per cent of the males, and 42.9 per cent of the females. Marked electrocardiographic abnormalities occurred in only 37.4 per cent of the males and in 40 per cent of the females.

It is believed that the hyperactive cardioinhibitory carotid-sinus reflex may be used as an aid in the diagnosis of coronary disease in persons of the coronary age who present suspicious complaints. As such, it is often of greater value than the

electrocardiogram, and will suggest the correctness of the diagnosis when the electrocardiogram may be entirely misleading.

The explanation for the frequency of the hyperactive reflex in coronary disease is, at the present state of knowledge, purely theoretical. It may be due to local ischemia in the heart, which lowers the resistance in the vagal ganglions and in the myoneural junctions, or which produces some chemical changes that sensitize the vagus nerves locally.

AUTHOR.

De Soldati, L., Cabanne, E. A., and Introzzi, A. S.: Determination of Blood Flow of the Fingers by the Plethysmographic Method. Rev. argent. de cardiol. 8: 383, 1942.

The blood flow through the fingers was recorded by the plethysmographic method in normal subjects and the influence of diverse stimuli was studied.

Immersion of both legs in cold water (15° C.) produced after a few minutes, first a decrease and then an increase in the blood flow which continued until after twenty minutes it reached the double of its initial value. Simultaneously a slight increase of the buccal temperature and a slight decrease of the cutaneous temperature occurred.

Immersion of both legs in hot water (45° C.) produced a definite increase of the blood flow, the maximum being attained after twenty minutes. Simultaneously the buccal temperature decreased and the cutaneous temperature increased. In the height of the vasodilatation thus obtained a deep inspiration was followed by a marked reduction of the blood flow. A loud noise produced the same effect.

Even in basal conditions the plethysmographic method shows that the blood flow to the fingers may be very different from one person to the other. But in the same subject, in different occasions, it is fairly uniform, thus justifying its use for the study of the peripheral circulation.

AUTHORS.

Semisch, C. W. III, and Merves, L.: Electrocardiographic Studies on Artificially Produced Pulmonary Artery Occlusion in Human Beings. Arch. Int. Med. 69: 417, 1942.

An electrocardiographic study is presented of fourteen cases of acute pulmonary artery occlusion in human beings incident to partial or complete unilateral pneumonectomy.

The significant changes in the electrocardiographic pattern produced by acute pulmonary artery occlusion in this study are: (1) shift of the electrical axis to the right, 71.4 per cent; (2) development of a deep S wave in Lead I, 50 per cent, and (3) staircase ascent of the RS-T segment in Lead II, 28.6 per cent. These changes tend to appear immediately after the occlusion and to disappear within twenty-four hours, but not constantly so.

The nature of the changes observed are such as to lend support to the belief that electrocardiographic changes associated with pulmonary embolism are produced by strain placed on the right ventricle.

Proper use and interpretation of electrocardiograms, bearing in mind their limitations, may be of help in differentiating pulmonary embolism at its onset from clinically similar diseases.

AUTHORS.

Hall, G. E., Stewart, C. B., and Manning, G. W.: The Electrocardiographic Records of 2,000 R. C. A. F. Aircrew. Canad. M. A. J. 46: 226, 1942.

The gross analysis of the electrocardiograms of 2,000 healthy male adults between the ages of 18 and 32 taken while at rest in the recumbent position has

been presented. It is fully appreciated that the value of electrocardiography in diagnosing cardiac conditions is limited. However, the numbers of records showing axis deviation, abnormalities of the T wave in Leads I and II, and the occurrence of prolonged P-R and QRS intervals indicate the value of such recordings at least as an indication for more careful investigation before selection for aircrew duties.

AUTHORS.

Öhnell, v. R. F.: Some Types of Electrocardiograms, Their Relation to Paroxysmal Tachycardia. Cardiologia 5: 321, 1941.

Some types of electrocardiograms (with abnormalities between the P and the R wave) have been described and, further, their relation to paroxysmal tachycardia and to the Wolff-Parkinson-White (''WPW'') syndrome has been discussed.

Type A.—Gradual rise of the initial part of the QRS complex in one lead. ''Conduction-time'' subnormal.

Type B.—Gradual rise of the intermediate part between the P wave and the ventricular complex in one lead.

AUTHOR.

Segall, H. N., and Goldbloom, A.: Atrio-Ventricular Nodal Paroxysmal Tachycardia in an Infant Treated With Acetyl Beta Methylcholine. Canad. M. A. J. 46: 233, 1942.

Atrioventricular paroxysmal tachycardia in an infant, aged 1 month, was treated with acetyl beta methylcholine. The first dose, 5 mg., administered during the second hour of the attack failed to restore normal rhythm but caused changes in amplitude of QRS and depression of S-T interval. The last dose, 8 mg., produced bradycardia (rate 20 to 56) by slowing abnormal rhythm for about five minutes, then normal rhythm was restored, but there were no changes in QRS and T waves. Adrenalin seems to be preferable to atropine in controlling the disagreeable systemic effects of acetyl beta methylcholine.

AUTHORS.

Kennedy, J. A., and Clark, S. L.: Observations on the Physiological Reactions of the Ductus Arteriosus. Am. J. Physiol. 136: 140, 1942.

The authors have established that the ductus arteriosus is a structure which can actively close in response to certain stimuli. It responds to local mechanical stimulation much the same as certain other hollow muscular structures by contracting. The authors do not believe that local mechanical stimulation has an essential role in its closure under physiologic conditions. Neither does a neurologic mechanism appear essential to closure following artificial inflation of the lungs. Their findings are at variance with those of Barcroft, Kennedy, and Mason (1938) with respect to the reaction of the ductus following stimulation of the vagus nerve, but they believe that the present observations have been adequately controlled.

Of the stimuli causing closure of the ductus which the authors have explored, it seems likely that under physiologic conditions breathing is the most important. The actual filling of the lungs by just any gas is not sufficient. From their experiments it appears that oxygen is a necessary component of the gas mixture since inflation of the lungs with pure nitrogen will not cause closure. Oxygen by vein will also cause closure without the necessity of accompanying inflation of the lungs. It is quite possible that many of all of the unexplained closures (see sec. 7) could be due to an increased oxygenation of the fetal blood in response to painful stimulation, struggling of the mother or fetus, hemorrhage, etc. There are other possible sources

of stimulation which the authors have not yet explored fully, such as various natural humoral substances, carbon dioxide, drugs, etc.

Such an influence as that of oxygen on the ductus may have something in common with the findings of Figge (1934), who demonstrated a definite effect on the metamorphosis of the aortic arches and gills in larval forms of the salamander by variations in oxygen tension of their environment.

If this seemingly important relationship of oxygen to the mechanism of closure of the ductus is true, it offers a practical indication for treatment of newborn infants, especially those which have difficulty in the oxygenation of their blood.

AUTHORS.

Castilla, C. R., and Aguirre, R. S.: Congenital Cardiac Block With Stokes-Adams Syndrome With Crises of Paroxysmal Ventricular Tachycardia and Terminal Fibrillation. Rev. argent. de cardiol. **8**: 340, 1941.

A case is described of congenital auriculoventricular block with syncopal attacks in a boy two and one-half years old. The electrocardiographic study showed that syncopal attacks were due to paroxysmal crises of prefibrillation ventricular tachycardia. The boy died of ventricular fibrillation.

AUTHORS.

Wising, P.: Familial, Congenital Sinus Tachycardia. Acta med. Scandinav. **108**: 299, 1941.

The author gives an account of four cases of permanent sinus tachycardia in two generations of a family in which this abnormality seems to occur as an hereditary anomaly.

AUTHOR.

Wood, P.: Congenital Pulmonary Stenosis With Left Ventricular Enlargement Associated With Atrial Septal Defect. Brit. Heart J. **4**: 11, 1942.

A case is described which presented the following features: pulmonary valvular stenosis, atrial septal defect, left ventricular dominance, and extreme permanent cyanosis.

The question arises whether this will prove a clinically recognizable congenital syndrome, or whether this is a freak case.

AUTHOR.

Garvin, C. F.: Infarction in Heart Disease. Am. J. M. Sc. **203**: 473, 1942.

Of 771 consecutive autopsied patients dead of heart disease, 354 (45.9 per cent) had one or more infarcts in the lungs, brain, kidneys, spleen, extremities and/or intestines. Subacute bacterial endocarditis was the type of heart disease most frequently associated with infarcts of the viscera, 80 per cent of the cases showing this complication. In coronary artery disease with myocardial infarction, about 60 per cent of the cases had one or more infarcts in the lungs, brain, kidneys, spleen, extremities and/or intestines. Coronary artery disease without myocardial infarction and rheumatic heart disease were about alike, approximately 50 per cent of the cases showing one or more infarcts. The incidence of infarction in hypertensive heart and syphilitic heart disease was about 40 per cent, and this complication was uncommon in cor pulmonale.

The lungs were involved by infarction in 28.7 per cent of the 771 cases, the kidney in 17 per cent, the spleen in 11.7 per cent, the extremities in 2.6 per cent, and the intestines in 1.7 per cent. There was infarction of the brain in 17.6 per cent of 432 examinations. The highest incidence of infarction occurred in subacute bacterial endocarditis (kidney, 70 per cent; and spleen 66.7 per cent).

The percentage of cases with one organ infarcted was 27.1; with two organs infarcted, 13.5; and with three or more, 5.3. The highest incidence of infarction of multiple viscera was in subacute bacterial endocarditis, 66.6 per cent of the cases having two or more organs infarcted.

AUTHORS.

Kutumbiah, P.: Rheumatism in Childhood and Adolescence. Indian J. Pediat. 8: 65, 203, 221, 1941.

The urgency and gravity of the rheumatic problem as it exists in India as yet to be realized by the medical profession and the public at large. Juvenile rheumatism ranks with syphilis, leprosy, and tuberculosis as one of the major problems of national health. In the past four decades much has been done to relieve the sufferings of the victims of leprosy and tuberculosis, by nation wide propaganda and organization. There is a great need for the institution of an active sustained crusade against rheumatic infection following the general principles similar to those successfully being employed against tuberculosis and leprosy. There is at present in existence a nucleus of an organization for controlling rheumatic infection. There are scattered about in the presidency various child welfare centers; in towns and cities there is medical inspection of schools, and in big cities we have adequately equipped and staffed hospitals for the treatment of the diseases of the throat and heart. Most of the work of these existing institutions is inco-ordinated. What is urgently required is to co-ordinate the activities of the existing institutions so that the organized supervision of children both at home and at school may be successfully achieved.

AUTHOR.

McDermott, W., Tompsett, R. R., and Webster, B.: Syphilitic Aortic Insufficiency: The Asymptomatic Phase. Am. J. M. Sc. 203: 202, 1942.

Aortic insufficiency due to syphilis is present in a clinically recognizable form for a relatively lengthy period of time (two to ten years) before the development of symptoms.

The asymptomatic form of aortic valvular syphilis is encountered in approximately one-half of the patients with valvular syphilis.

Present-day prognostic data, based as they are on the course following the onset of symptoms of failure, are inapplicable to this large group of patients with cardiovascular syphilis.

There are no available data on the ultimate length of this asymptomatic phase, but it appears from a study of our cases thus far that it can be measured in terms of years rather than months.

AUTHORS.

Pasqualini, R. Q., Lascalea, M. C., and Matera, R. F.: Syphilic Aortic Valvulitis and Subacute Bacterial Endocarditis. Rev. argent. de cardiol. 8: 392, 1942.

A case with necropsy is described of subacute bacterial endocarditis, superimposed on a syphilitic aortitis and valvulitis. Recent studies have shown that this is not a rare association as was formerly thought.

AUTHORS.

Isenhour, C. E., Kuder, K., and Dill, L. V.: The Effect of Parity on the Average Blood Pressure and on the Incidence of Hypertension. Am. J. M. Sc. 203: 333, 1942.

No demonstrable difference can be noted in the incidence of hypertension and the average blood pressure levels of parous and mulliparous women.

It seems likely that the hypertension and hypertension-producing diseases which occur following a large portion of the "toxemias of pregnancy" are not the result

of this complication of pregnancy, but rather that this complication of pregnancy occurs for the most part, if not exclusively, in patients whose vascular systems are endowed with the tendency toward hypertensive disease.

AUTHORS.

McLennan, C. E., McLennan, M. T., and Landis, E. M.: The Effect of External Pressure on the Vascular Volume of the Forearm and Its Relation to Capillary Blood Pressure and Venous Pressure. J. Clin. Investigation **21**: 319, 1942.

The pressure plethysmograph was used to determine the effect of graded external pressure on the vascular volume of the forearm, for the purpose of determining the usefulness of this procedure in estimating the blood pressure in the minute vessels collectively.

With external pressures ranging from 0 to 90 mm. Hg, pressure-volume curves were determined in twenty normal subjects (a) by suddenly arresting the circulation to the forearm and measuring decrease in volume during the ensuing mild hyperemia. The term ''dynamic vascular volume'' was used to indicate that the volume of blood in actual movement was being measured under these conditions.

In the normal forearm ''dynamic vascular volumes'' were greatest when external pressure was between 15 and 35 mm. Hg, becoming less at external pressures above and below this range.

To record the relation between ''dynamic vascular volume'' and external pressure in the form of a single numerical value, an objective method of analyzing the pressure-volume curves was adopted. The single value thus obtained was termed P_{mvc} and was defined as ''that external pressure at which the vis a tergo of the circulation is able to keep open the greatest collective dynamic vascular volume.''

P_{mvc} determined in the forearms of twenty normal subjects with the forearm segement at heart level and at 34° C. was 27, 21 and 21 mm. Hg by Methods I, II, and III respectively. Reasons are given for regarding Methods I and II as the most useful. In the normal subject the results by all three methods had roughly the same order of magnitude as average capillary blood pressure when determined directly.

This similarity between P_{mvc} and directly determined capillary blood pressure held also when the latter was reduced by elevating the forearm or increased by known venous congestion and by depressing the forearm below heart level.

With due precaution against assuming too quickly the quantitative validity of any indirect method of measuring intravascular pressure, it is suggested that the plethysmographic method may be useful in studying the volume of blood and the pressure in the minute vessels of the forearm in clinical conditions.

AUTHORS.

Flaxman, Nathan: Hypertensive Heart Disease of 10 to 20 Years' Duration; Report of 11 Cases. Ann. Internal Med. **15**: 821, 1941.

Eleven cases of hypertensive heart disease in patients who lived ten to twenty years (average 13.7 years) after the onset of the first cardiac symptoms are reported. They were of all ages from 25 to 70 years and had various cardiac rhythmic and conduction disturbances, neither factor apparently influencing the longevity.

AUTHOR.

Richards, D. W., Jr., Cournand, A., Darling, R. C., Gillespie, W. H., and Baldwin, E. DeF.: Pressure of Blood in the Right Auricle in Animals and in Man: Under Normal Conditions and in Right Heart Failure. Am. J. Physiol. **136**: 115, 1942.

In the study of venous pressures in one chimpanzee and a series of dogs, the development of right heart failure associated with acute pulmonary edema was accompanied not only by rise of peripheral and right auricular pressures, but also

by a disappearance of the normal pressure gradient between peripheral veins and right heart, the right auricular and peripheral venous pressure levels becoming nearly equal.

In nine human subjects with apparently normal circulations, right auricular pressure was recorded directly by means of right heart catheterization. The average gradient from arm to heart was +41 mm. of water. In six subjects absolute pressure levels at the right auricle were determined by locating the position of the catheter by lateral x-ray; the average right auricular pressure (subjects supine) was +37 mm.

Three patients in congestive heart failure, with high peripheral venous pressures, showed decrease in peripheral-central pressure gradients, the pressures in arm vein and in right auricle being almost identical.

AUTHORS.

Hardy, A. G., and Denham, H. E. H.: Popliteal Aneurysm. Report of a Bilateral Case Treated by Bilateral Excision. Guy's Hosp. Rep. **90**: 244, 1941.

A case of bilateral popliteal aneurysm is described. Methods of investigating the condition of the aneurysm and, more particularly the collateral circulation of the limb, are discussed.

On one side spontaneous thrombosis had occurred with intensification of symptoms. Excision of the aneurysm under local anesthesia was followed by uneventful recovery, presumably due to establishment of an adequate collateral circulation. Excision of the aneurysm on the opposite side was followed by threatened gangrene which was only narrowly averted.

The various forms of alternative operations are discussed and the arguments in favor of the modern treatment by excision of the aneurysm are put forward.

We have been unable to find a report in the literature of any other case of successful bilateral resection of a popliteal aneurysm.

AUTHORS.

Keen, J. A.: The Collateral Venous Circulation in a Case of Thrombosis of the Inferior Vena Cava, and Its Embryological Interpretation. Brit. J. Surg. **29**: 105, 1941.

A rare case of thrombosis of the inferior vena cava with fibrous tissue formation and calcification is described, together with x-ray findings and accounts of the microscopic sections of the thrombosed vessel and of the kidney showing the perinephric venous circulation. The collateral circulation which became established in the posterior abdominal wall is traced and illustrated. The literature on the development of the inferior vena cava is reviewed, and this is followed by an embryologic explanation of the collateral circulation on the basis of a simplified ground plan.

AUTHOR.

Price, P. B., Sloan, H. E., Jr., and LaRochelle, F. T.: A Study of Mechanical Factors in the Circulation, With Special Reference to the Problem of Acute Circulatory Failure. Bull. Johns Hopkins Hosp. **52**: 26, 1942.

Many features of the normal blood circulation have been reproduced in a mechanical circulation model, and certain changes which characterize acute circulatory failure have been studied experimentally in the machine and in dogs. The behavior of the machine under controlled conditions provides a number of suggestive clues to the complex problem of hemodynamics. The general impression received by the authors is that the living circulation is influenced by mechanical factors to a degree not generally appreciated heretofore.

The mechanical circulation is essentially a series of fluid-filled, pressure reservoirs in dynamic equilibrium. When this balance is upset by external factors, the machine

tends automatically to establish a new equilibrium by redistributing its circulating fluid between the different vascular compartments. It is suggested that under analogous conditions similar adjustments take place in the animal.

On the basis of this study the following statements are believed to express general principles in hemodynamics: blood pressure has a definite relationship to the elasticity and distension of the vascular system; changes in peripheral resistance tend to have opposite effects upon arterial pressure and cardiac output; effects of postural changes upon regional and general blood flow depend upon the degree of dilatation or collapse of blood vessels produced by the variations in hydrostatic pressure, as well as upon the efficiency of venous valves and the pumping action of respiration and other muscular movements; peripheral resistance varies with velocity of flow, viscosity of blood, and size of blood channels.

The view that acute circulatory failure, such as occurs in shock, may be due to a disparity between blood volume and vascular capacity is criticized.

The concept of a minimum effective blood volume is introduced, and reasons are suggested why comparable persons vary so greatly in blood volume, in susceptibility to blood loss, and in response to blood transfusion.

AUTHORS.

McIntosh, R.: Circulatory Failure in Acute Glomerulonephritis. Canad. M. A. J. 46: 445, 1942.

One of the clinical features of acute glomerulonephritis, namely, the accompanying picture of circulatory failure, is discussed. Although its presence is in no sense difficult to recognize when the symptoms and signs are well marked, the frequency of its occurrence in relatively mild degree has only recently come to be appreciated, and the question is fairly raised whether it is always given due weight in the evaluation of a given clinical situation. Because of its importance in determining the outcome in some of the cases of acute nephritis which prove fatal early in the attack, the necessity of sparing the heart any unwarranted burden should be borne in mind in all cases—even the mildest ones.

AUTHOR.

Ane, J. N., and Burch, George E.: Effects of Roentgen Irradiation Upon Linear Rate of Flow in Cutaneous Lymphatics of Humans. Proc. Soc. Exper. Biol. & Med. 48: 471, 1941.

Data obtained from seven human beings indicated that small doses of roentgen irradiation (220-450 r) to the skin are not likely to disturb the linear flow of lymph in the cutaneous lymphatics, while large doses sufficient to produce a first degree skin reaction probably will reduce the rate of lymph flow.

AUTHORS.

King, A. B.: Demonstration of the Basilar Artery and Its Branches With Thorotrast. Bull. Johns Hopkins Hosp. 52: 81, 1942.

The basilar artery and its branches were successfully demonstrated in a living human subject by means of thorotrast. There were no untoward reactions. The procedure should be considered in patients when the differential diagnosis includes aneurysms or defects of these vessels.

AUTHOR.

Brock, R. C.: Experiences in Pulmonary Artery Ligation. Guy's Hosp. Rep. 90: 217, 1941.

The historical development of pulmonary artery ligation is mentioned; the first deliberate dissection of the main vessels was by Rienhoff in July, 1933. The opera-

tive approach is discussed and the posterolateral incision recommended; an anterior approach does not give room enough to make the necessary manipulations with full freedom and safety.

Infiltration of the hilum with local anesthetic is advised in order to diminish harmful stimuli and to facilitate dissection. A description of the operation in the two sides is given; the exposure on the left side is much easier than on the right.

The exposure of the right pulmonary artery is made much easier by recognition of a constant triangular facial fold passing from behind the lowest part of the superior vena cava across the front of the right pulmonary artery. This fold can be divided with impunity. Its division both frees the vena cava for retraction medially and exposes the stem of the right pulmonary artery. This triangular bloodless fold has not been described or deputed before.

Mention is made of direct estimation of the pulmonary blood pressure in man. Direct estimation before and after ligation shows no change in the arterial pressure demonstrating that compensation is immediate and that simple back pressure on the heart is not the cause of death or grave illness in pulmonary embolism. This is an original observation in man.

The effects of ligature of the right or left pulmonary artery without removal of the lung are discussed; sloughing is prevented by the bronchial arteries.

In the eighteen cases in which pulmonary artery ligation was performed no direct ill effect could be attributed (except for one in which death followed a slipped ligature). The tying of the artery produces no observable clinical effect; the pulse rate remains unaltered and neither the pulmonary nor the systemic blood pressure changes. In the last twelve cases accompanied by pneumonectomy, only two deaths occurred and these were both three weeks after operation; in one case from a lung abscess, in the other from pericarditis. The ability of the cardiovascular system to accommodate itself rapidly to the profound changes caused by sudden shutting off of one-half of the pulmonary arterial system is thus amply proved.

AUTHOR.

Wiggers, H. C., Duschatko, A. M., and Kory, R. C.: The Circulatory Response of the Unanesthetized Dog to Small Physiological Quantities of Adrenalin. Am. J. Physiol. **136**: 87, 1942.

It appears that the unanesthetized dog will exhibit either an elevation or a depression of blood pressure in response to small intravenous injections of adrenalin, the direction depending upon the dose per unit of animal weight. The depressor reaction, which can be uniformly elicited by 0.1 μg./kg. per kilogram quantities, is reproducible in the same dog at twenty-minute intervals. Shorter intervals were not investigated. Slightly stronger concentrations of this drug may elicit either pressor or depressor effects, the latter being slightly more prevalent. Although the factors which govern the direction of the response are not completely understood, it is suspected that the initial emotional status of the animal is of considerable importance. The rate of injection does not appear to influence the direction of the response.

Since the depressor response is characterized by a predominant reduction of systolic pressure, it becomes increasingly difficult to accept the doctrine that a diminution of systemic peripheral resistance is the precipitant mechanism. We are more inclined to postulate an initial dilatation of pulmonary vessels with a consequent reduction of pulmonary arterial resistance and thus a temporary pooling of blood within the lung vessels. Hence, a transient reduction of left ventricular filling will ensue which will be further accentuated by the simultaneous tachycardia.

It has also been suggested that adrenalin may augment the capacity of the aorta and its immediate large branches. This would also exert directional effects upon the pulse pressure pattern similar to those resulting from a reduced stroke volume of the

left ventricle. These two mechanisms may even act synergically in bringing about the adrenalin depression of arterial blood pressure.

AUTHORS.

Gootnick, A., Saland, G., Klein, C., and Zurrow, H.: Studies on Vasodilatation Tests in Peripheral Vascular Disease. J. Lab. & Clin. Med. **27**: 878, 1942.

In the study of the patient who presents himself with symptoms referable to the peripheral arterial tree, all three tests discussed have a place. The place for each is indicated in the results the authors have summarized in the accompanying tables.

Sodium nitrite injected intravenously and the hot water bath are both useful as preliminary tests for vasospasm. Of the two, the thermal test is better suited to patients with vascular involvement when we wish to discover the degree of associated vessel spasm. In patients who give the clinical impression of nonorganic vasopastic involvement the nitrite test is considerably more dependable. It is also feasible for patients prone to syncope in a hot bath.

In this clinic a patient whose vasodilatation in response to either of these tests reaches normal values is then regarded as possessing normal vascular reserve. Those who respond to either of these tests with subnormal vasodilatation are then tested with peripheral nerve block. The advantage of this scheme is that in a considerable proportion of patients a simple, nonmanipulative procedure serves adequately to reveal the intensity of spasm and the vascular reserve of the limb in question. Nerve block is reserved as the test of last appeal for those patients in whom either the thermal stimulus or the sodium nitrite failed to induce fully normal vasodilatation.

AUTHORS.

Spealman, C. R.: The Action of Ions on the Mammalian Heart. Am. J. Physiol. **136**: 332, 1942.

In the guinea pig right atrium preparation, certain depressive or abnormal changes, such as a decrease in rate which was usually progressive, a depression of the amplitude of contraction, or arrhythmia, occurred when the concentration of the various ions was too different from normal. Within limits close to normal, the most definite positive effect was the variation of the amplitude of contraction with the Ca ion concentration. There was also some suggestion that increasing the Ca ion concentration caused an increase in the duration of the response, while increasing the K ion concentration caused a decrease in the duration of the response.

In the Langendorff preparation of the guinea pig heart, the heart rate was independent of the K ion and Ca ion concentrations within regions close to normal, but was depressed in certain instances where the concentration was too different from normal. The P-R interval lengthened as the Ca ion concentration increased, and shortened as the K ion concentration increased. The Q-T interval was lengthened as the Ca ion concentration decreased, but was not greatly affected by changing the K ion concentration.

In the acute experiments on dogs, in which the plasma Ca concentration was varied, the intraventricular pressure, the P-R interval, and the height of the P wave all tended to vary in the same sense with the plasma Ca concentration. The duration of response was slightly decreased and the heart rate was increased when the plasma Ca concentration was raised. The Q-T interval, the height of the R wave, and the height of the T wave showed no very definite tendencies to vary with the plasma Ca concentration.

In the acute experiments on dogs in which the plasma K concentration was varied, the intraventricular pressure and the height of the T wave tended to vary in the same sense and the P-R interval in the opposite sense with the plasma K concentration. The magnitude of the intraventricular pressure changes was small. The duration of response was slightly decreased when the plasma K concentration was raised. The

heart rate, the Q-T interval, the height of the P wave, and the height of the R wave showed no definite tendencies to vary with the plasma K concentration.

AUTHOR.

Zwemer, R. L., and Arrighi, F. P.: Modification of the Activity of the Heart of the Frog Produced by Chloride of Potassium. Rev. argent. de cardiol. 8: 301, 1941.

Toads injected intraperitoneally with a lethal dose (1 c.c. per 100 Gm. weight) of a 10 per cent solution of potassium chloride and with a nonlethal dose (1 c.c. per 100 Gm. weight) of a 6 per cent solution, develop important cardiac alterations which are permanent in the former and transient in the latter. The following observations were made:

1. The activity of the sinus is depressed and bradycardia is observed.
2. The activation of the myocardium is slow as shown by broadening of P-R and B waves.
3. The excitability of the heart decreases as shown by an increase of rheo base and chronaxie.
4. Other alterations in the activation of the myocardium manifest themselves by variations in the order of activation of the chambers of the heart, irregularities of P and R, appearance of an S wave, ventricular fibrillation, electrical alternation, extrasystoles, etc.
5. The recovery phase of each beat is disturbed because T becomes irregular diphasic or negative.
6. These cardiac alterations are fairly parallel to the general disturbance (asthenia, loss of reflexes) and the toads injected with nonlethal dose of potassium chloride recover the normal cardiac and general state.

AUTHORS.

Flaxman, N.: Clinical Value of Digitalis in Hypertensive Heart Failure. I. With a Normal Rate and a Regular Rhythm. Am. J. M. Sc. 203: 741, 1942.

The study of 160 cases of hypertensive heart failure with a normal rate and a regular rhythm is reported.

The age of the patient and the duration of the symptoms before treatment with digitalis apparently had no influence on the outcome.

Of all the hypertensive patients who develop congestive heart failure, those with isolated failure of the left ventricle, a normal heart rate, and a regular rhythm have the best prognosis.

Factors over which digitalis itself had no control, such as uremia, coronary thrombosis, and cerebral hemorrhage, caused twenty-two (64 per cent) of the thirty-seven deaths in this series of 160 cases.

Treatment with digitalis may be regarded as most successful in these decompensated hypertensive patients, despite the normal rate and the regular rhythm.

AUTHOR.

Corrigendum

In the May, 1942, issue of the JOURNAL, Vol. 23, page 636, the discussion of Dr. William S. Collens should have read as follows:

I should like to congratulate the authors and wish to say that Dr. Boas and I recently conducted the same kind of studies and came to the same conclusions. We used the apparatus which we devised for intermittent venous occlusion, and modified it by attaching four cuffs. Three cuffs were inflated at one time while one cuff was deflated in sequence.

Book Review

ESSENTIALS OF ELECTROCARDIOGRAPHY: By Richard Ashman, Ph.D., Professor of Physiology, and Edgar Hull, M.D., Professor of Medicine, Louisiana State University Medical Center. The Macmillan Company, New York, 1941, ed. 2, 373 pages, 122 illustrations, $5.00.

Like many other developments in medicine, the practical application of electrocardiography has outrun our knowledge of some of its fundamental concepts. Every student of the subject is tortured by dissatisfaction with his grasp of these fundamental facts. Worse still, many of us who are lacking in adequate discipline in the sciences of mathematics and electricity are scarcely able to comprehend reports of research in electrocardiography whose basis implies an understanding of those sciences. This text represents a unique attempt to express essential researches bearing on fundamental electrophysiologic concepts underlying this subject in terms that are comprehensible to any earnest student. The first seventy-five pages are devoted to this, but, throughout the text, in the consideration of various electrocardiographic phenomena, explanations are given which refer the reader to these basic concepts. If nothing more than this had been done, it would justify bringing out a second edition of this book. However, the discussion of fundamentals would gain in clarity and would be more widely comprehended if greater use of diagrams had been made.

The next section of the book considers the components of the auricular and ventricular complexes. These are treated in the order of their occurrence, normal characteristics are described, limits of normal variation indicated, and changes produced by disease are stated. Two chapters deal with disturbances of the cardiac mechanism.

The remainder of the book deals with the electrocardiogram in diseases of the heart. This discussion is well organized and is of great practical importance. However, some subjects suffer from too brief a treatment. In other instances, more electrocardiograms to indicate variations within a given pattern would have been desirable for greater clarity.

The reviewer would take mild exception to such statements as, "The recognition of early and relatively mild changes in the myocardium may be, we believe, greatly facilitated if the electrocardiographer pays more attention to minor deviations from normal." This is "heady medicine," and tends to encourage those who make too much of too little in the interpretation of electrocardiograms. Anyone who fathers a book on this subject is chagrined more by those who see too much in a tracing than by those who see too little. More emphasis on the unreliability of the electrocardiogram as a means of excluding the possibility of coronary sclerosis or of establishing such a diagnosis unless previous acute myocardial infarction had occurred would have served a useful purpose, in my opinion.

Despite these minor criticisms this book deserves a wide circulation. It is clearly written and generally sound, and will furnish safe guidance for the student and practitioner; no one can read its chapters on the fundamental basis of electrocardiography without a feeling of gratitude to the authors.

A. R. BARNES.

American Heart Association, Inc.

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THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of twenty-seven eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is $5.00. Journal membership at $11.00 includes a year's subscription to the AMERICAN HEART JOURNAL (January-December) and annual membership in the Association. The Journal alone is $10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

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